

# PATENT COOPERATION TREATY

14

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>X-12420</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/US00/16319</b>	International filing date (day/month/year) <b>11/07/2000</b>	Priority date (day/month/year) <b>19/07/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D209/22</b>		
Applicant <b>ELI LILLY AND COMPANY et al</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.  
  
☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of 136 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>[19/01/2001] 24.01.01</b>	Date of completion of this report <b>28.06.2001</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Feiler, L</b>  Telephone No. <b>+49 89 2399 8282</b>  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/16319

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-109 as received on 13/06/2001 with letter of 11/06/2001

**Claims, No.:**

1-26 as received on 13/06/2001 with letter of 11/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
  - ☐ the language of publication of the international application (under Rule 48.3(b)).
  - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
  - ☐ filed together with the international application in computer readable form.
  - ☐ furnished subsequently to this Authority in written form.
  - ☐ furnished subsequently to this Authority in computer readable form.
  - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
  - ☐ the claims, Nos.:
  - ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:  
**see separate sheet**

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-18, 21-26.

because:

- ☒ the said international application, or the said claims Nos. 22, 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-18, 21, 24-26.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 19, 20
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 19, 20
Industrial applicability (IA)	Yes: Claims 19, 20

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No: Claims

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/16319

1. With letter of 11/06/01 the Applicant has filed a "replacement application comprising description pages 1-109 and Claims 1-26. It would appear that these documents do not indicate the amendments indicated in the response to the written opinion dated 16/03/0; they are essentially identical to the document originally filed.

2. Claims 22 and 23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

It has to be stressed that subject matter of Claims 1-18 has not been searched completely. Consequently, the following observations apply to **subject matter of Claim 19** and dependent claims only.

### **3. Cited Documents**

EP-A-0675110= D1

EP-A-0620215= D2

US-A-5684034= D3

WO-A-0037358= D4

WO-A-9921559= D5

WO-A-9921546= D6

EP-A-0952149= D7

WO-A-9637469= D8

WO-A-9106537= D9

J. Med. Chem. 39(1996), pp. 5119-5139= D10

The indicated designation will be used throughout the examination procedure.

D4 and D7 are P-documents.

### **4. Novelty**

The subject-matter of Claim 19 differs from D1 essentially due to the fact that the 4-position of the indole moiety is substituted by an acidic group (e.g. -COOH) whereas the corresponding position of the compounds of Claim 19 of the application comprises a carbamoyl group.

D2, D3 and D6 disclose indole-3-acetamid derivatives whereas the compounds of Claim 19 of the application are indole-3-glyoxylamides.

According to D4 the 3-indole substituent is an oxime amide or oxime thioamide. D5 refers to a specific indol-4-yloxyacetic morpholino-N-ethylester.

D7 discloses carbazole derivatives, D8 refers to N-benzylindol-3-yl propanoic acid, D10 discloses indole-3-acetamides and D9 comprises indole derivatives not considered according to the application.

The subject-matter claimed can therefore be considered novel.

## **5. Inventive Step - Breadth of Claims**

### **5.1 Subjective Problem**

According to the application (p. 1, first paragraph and page 2, lines 14-16) the problem underlying the invention is to be seen in the provision of further compounds which are inhibitors of mammalian secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) and are therefore useful to treat inflammatory diseases.

### **5.2 Relevant and closest prior art**

Documents D1-D3, D5, D6, D9 and D10 are considered to be relevant for the assessment of inventive step since these compounds come structurally close to those comprised by Claim 19 of the application and also have the same qualitative activity. If the claimed priority date is not valid D4 may also come into picture.

The closest prior art is given by D1.

### **5.3 Objectively solved problem**

The application documents disclose the test methodology and quantitative test data according to the table of page 109 so that it can be said that at least the tested compounds solve the problem defined above.

### **5.4 Evaluation of the solution of the problem**

D1-D3, D5, D6, D9 and D10 disclose compounds structurally very similar to those of the present application.

The products of those documents also solve the problem of providing compounds which inhibit mamalian sPLA<sub>2</sub>.

The person skilled in the art seeking a solution to the problem defined above would therefore have been prompted to consider further derivatives of compounds which are already known to solve the above defined problem. In this context it is to be stressed that e.g. D1 discloses that the R<sup>4</sup> corresponding substituent is an acidic group e.g. the -COOH group, but D5 and D6 disclose that this group can be derivatisised (ester functions) without changing the qualitative activity. In other words the compounds of D5

and D6 could be considered as prodrugs of D1-compounds. Consequently, the compounds of the invention being amide derivatives are to be considered as further prodrugs of D1-compounds.

The person skilled in the art would have been able to infer that a modification of the proposed type would have no effect on the activity profile so that he would have considered the proposed solution in the expectation of success.

The solution of the technical problem defined in point 5.1 according to the application is therefore obvious in the light of the prior art and thus the subject-matter of the present Claim 19 cannot be considered to be inventive.

## **6. Industrial applicability**

For the assessment of the present claims 22 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

## **7. Clarity**

- In Claim 19 (L<sub>4</sub>) remains undefined
- Claim 20 appears twice; specific compounds are claimed in the second Claim 20 already claimed in the first one; this is considered to be superfluous and should be avoided.
- Claim 24 is unclear.

## **8. Suggestions**

In a possible national or regional examination procedure an inventive step could possibly be acknowledged should comparative data be submitted which show that apart from the technical problem defined in point 4.1 another, e.g. more exacting, problem, which can be derived from the application as originally filed (e.g. surprising improvement), existed and has actually been solved by originally disclosed technical

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features, which would need to be incorporated in Claim 19.

In this respect it should be borne in mind that the compounds of the closest prior D1 must bear the closest possible structural resemblance in order that the comparison be valid. A suitable comparison would be e.g.:

Examples 1 and 17 of D1 versus corresponding compounds of the application whereby all possible variations should be included.

The breadth of the claims should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based.

Even if it turns out that the tested compounds of page 109 solve the problem defined in point 8, first paragraph the proposed broadness goes far beyond of what could be considered to be a reasonable generalisation:

$L_4$  is always  $-OCH_2-$ ;

$R_b$  is the residue of simple amino acids only;

$(R_{13})_1$  is always H;

$R_{16}$  is H and

$R^{22}$  is an alkyl only.

It is not reasonable e.g. to define  $NR_b$  as "an amino acid residue of a natural or unnatural amino acid" or to define  $L_4$  (which was obviously intended to mean (Lc)) other than  $-OCH_2-$ .

The description should be adapted to new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by Claim 1 are to be deleted.

All the documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.



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Novel sPLA<sub>2</sub> InhibitorsField of the Invention

This invention relates to novel indole compounds  
5 useful for Inflammatory Diseases.

Background of the Invention

The structure and physical properties of human non-  
pancreatic secretory phospholipase A<sub>2</sub> (hereinafter  
10 called, "sPLA<sub>2</sub>") has been thoroughly described in two  
articles, namely, "Cloning and Recombinant Expression of  
Phospholipase A<sub>2</sub> Present in Rheumatoid Arthritic  
Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski,  
Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.;  
15 Kloss, Jean; and Johnson, Lorin K.; The Journal of  
Biological Chemistry, Vol. 264, No. 10, Issue of April  
5, pp. 5335-5338, 1989; and "Structure and Properties of  
a Human Non-pancreatic Phospholipase A<sub>2</sub>" by Kramer, Ruth  
M.; Hession, Catherine; Johansen, Berit; Hayes,  
20 Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard,  
Richard; and Pepinsky, R. Blake; The Journal of  
Biological Chemistry, Vol. 264, No. 10, Issue of April  
5, pp. 5768-5775, 1989; the disclosures of which are  
incorporated herein by reference.

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It is believed that sPLA<sub>2</sub> is a rate limiting nzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA<sub>2</sub> mediated release of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA<sub>2</sub>; such as sepsis or rheumatoid arthritis.

It is desirable to develop new compounds and treatments for sPLA<sub>2</sub> induced diseases.

#### Summary of the Invention

This invention provides novel indole compounds having potent and selective effectiveness as inhibitors of mammalian sPLA<sub>2</sub>.

This invention is also the use of novel indole compounds useful in the treatment and prevention of Inflammatory Diseases.

This invention is also the use of novel of indole compounds to inhibit mammalian sPLA<sub>2</sub> mediated release of fatty acids.

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This invention is also a pharmaceutical composition containing any of the indole compounds of the invention.

5    **I.    Definitions:**

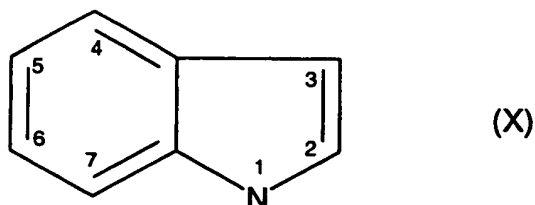
          The term, "Inflammatory Diseases" refers to diseases such as inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic  
10    fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or  
15    juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes",  
20    polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism,  
25    bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing),

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miscellaneous forms of arthritis, neuropathic joint  
disease (charco and joint), hemarthrosis (hemarthrosic),  
Henoch-Schonlein Purpura, hypertrophic osteoarthropathy,  
multicentric reticulohistiocytosis, arthritis associated  
5 with certain diseases, surcoilosis, hemochromatosis,  
sickle cell disease and other hemoglobinopathries,  
hyperlipoproteineimia, hypogammaglobulinemia,  
hyperparathyroidism, acromegaly, familial Mediterranean  
fever, Behat's Disease, systemic lupus erythrematosis,  
10 or relapsing polychondritis and related diseases which  
comprises administering to a mammal in need of such  
treatment a therapeutically effective amount of the  
compound of formula I in an amount sufficient to inhibit  
sPLA<sub>2</sub> mediated release of fatty acid and to thereby  
15 inhibit or prevent the arachidonic acid cascade and its  
deleterious products.

The term, "indole nucleus" refers to a nucleus  
(having numbered positions) with the structural  
20 formula (X):



The indole compounds of the invention employ  
certain defining terms as follows:

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The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary  
5 butyl, sec-butyl, n-pentyl, and n-hexyl.

The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated  
10 number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group  
15 containing only carbon and hydrogen.

The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or  
20 unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrrolodiny, piperidiny, furanyl,  
25 thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl,

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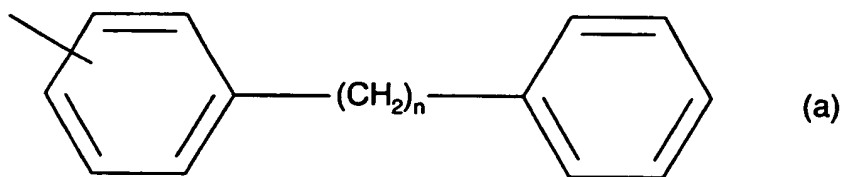
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indolyl, carbazolyl, norharmanyl, azaindolyl,  
benzofuranyl, dibenzofuranyl, dibenzothiophenyl,  
indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl,  
anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl,  
5 benzothiazolyl, purinyl, pyridinyl, dipyridyl,  
phenylpyridinyl, benzylpyridinyl, pyrimidinyl,  
phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl,  
phthalazinyl, quinazolinyl, morpholino, thiomorpholino,  
homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl,  
10 oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,  
tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-  
dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidyl,  
hexamethyleneiminium, heptamethyleneiminium, piperazinyl  
and quinoxalinyl.

15

The term, "carbocyclic radical" refers to radicals  
derived from a saturated or unsaturated, substituted or  
unsubstituted 5 to 14 membered organic nucleus whose ring  
forming atoms (other than hydrogen) are solely carbon  
20 atoms. Typical carbocyclic radicals are cycloalkyl,  
cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl,  
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,  
indenyl, stilbenyl, terphenyl, diphenylethylenyl,  
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,  
25 biphenyl, bibenzyl and related bibenzyl homologues  
represented by the formula (a):

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where n is a number from 1 to 8.

5        The term, "non-interfering substituent", refers to radicals suitable for substitution at positions 4,5,6 and/or 7 of the indole nucleus and on other nucleus substituents (as hereinafter described for Formula I), and radicals suitable for substitution on the

10 heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>7</sub>-C<sub>12</sub> aralkyl, C<sub>7</sub>-C<sub>12</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>2</sub>-C<sub>8</sub>

15 alkenyloxy, C<sub>2</sub>-C<sub>8</sub> alkynyloxy, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyloxy, C<sub>2</sub>-C<sub>12</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>12</sub> alkylcarbonylamino, C<sub>2</sub>-C<sub>12</sub> alkoxyamino, C<sub>2</sub>-C<sub>12</sub> alkoxyaminocarbonyl, C<sub>1</sub>-C<sub>12</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>2</sub>-C<sub>12</sub> alkylthiocarbonyl, C<sub>1</sub>-C<sub>8</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>8</sub>

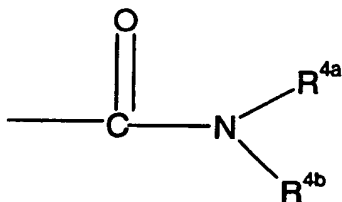
20 alkylsulfonyl, C<sub>2</sub>-C<sub>8</sub> haloalkoxy, C<sub>1</sub>-C<sub>8</sub> haloalkylsulfonyl, C<sub>2</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, -C(O)O(C<sub>1</sub>-C<sub>8</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C<sub>1</sub>-C<sub>8</sub> alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino,

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bromo, carbamyl, carboxyl, carbalkoxy,  $-(CH_2)_n-CO_2H$ ,  
chloro, cyano, cyanoguanidiny1, fluoro, guanidino,  
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,  
iodo, nitro, phosphono,  $-SO_3H$ , thioacetal, thiocarbonyl,  
5 and carbonyl; where n is from 1 to 8 and R is C<sub>1</sub>-C<sub>8</sub>  
alkyl.

The term, "organic substituent" refers to a  
monovalent radical consisting of carbon and hydrogen  
10 with or without oxygen, nitrogen, sulfur, halogen, or  
other elements. Illustrative organic substituents are  
C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>7</sub>-C<sub>14</sub> aralkyl, C<sub>7</sub>-C<sub>14</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub>  
cycloalkyl, C<sub>1</sub>-C<sub>8</sub> alkoxyalkyl and these groups  
substituted with halogen,  $-CF_3$ ,  $-OH$ , C<sub>1</sub>-C<sub>8</sub> alkyl, amino,  
15 carbonyl, and  $-CN$ .

The term, "acylamino acid group" is represented by  
the formula:



20 wherein R<sup>4a</sup> is selected from the group consisting of H,  
(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl,  $-CF_3$ ;  
and wherein NR<sup>4b</sup> is an amino acid residue with the



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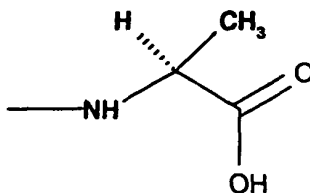
nitrogen atom being part of the amino group of the amino acid. A typical amino acid is selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine, asparagine, cystein, glutamine, 5 glutamic acid, histidine, lysine, methionine, serine, threonine, tryptophan, tyrosine and derivatives thereof. Also contemplated within the definition of amino acid is *l*-proline, *d*-proline and derivatives thereof. Also contemplated within the definition of amino acids are 10 peptides, polypeptides and derivatives thereof.

The term "substituted group" is an organic group substituted with one or more non-interfering substituents.

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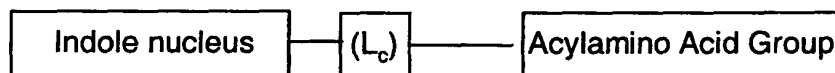
The terms, "amino acid residue" refer to the portion of the amino acid group coupled at the nitrogen atom of the amino terminus. It is the amino acid less a hydrogen atom from the amino terminus. It is further 20 illustrated as used herein for the amino acid alanine attached at the nitrogen atom as shown below:

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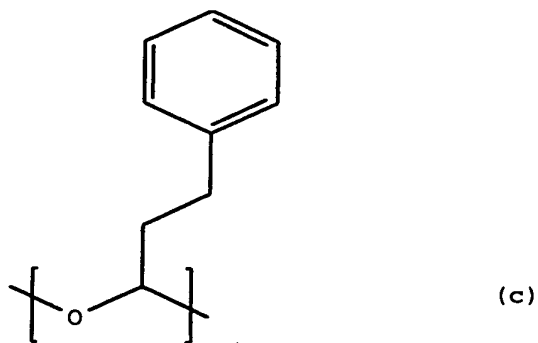
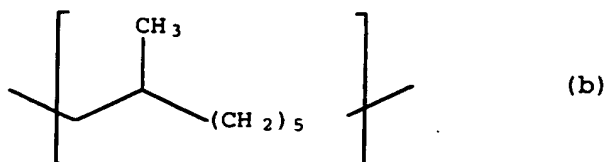
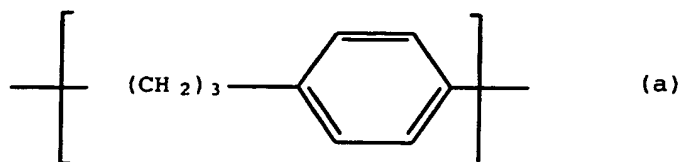
The words, "acylamino acid linker" refer to a divalent linking group symbolized as,  $-(L_C)-$ , which has the function of joining the 4 - position of the indole nucleus to an acylamino acid group in the general

5 relationship:



The words, "acylamino acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group  $-(L_C)-$  that connects the 4 -  
10 position of the indole nucleus with the acylamino acid group. The presence of a carbocyclic ring in  $-(L_C)-$  counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2  
15 atoms in calculating the length of  $-(L_C)-$ . Illustrative acylamino acid linker groups are;

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wherein, groups (a), (b) and (c) have acid linker lengths of 5, 7, and 2, respectively.

5

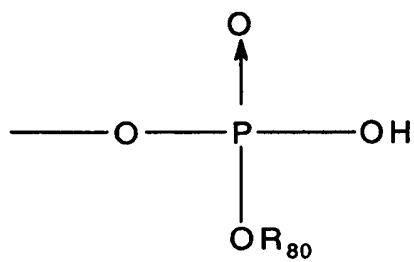
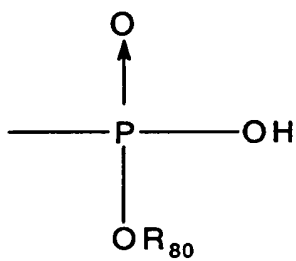
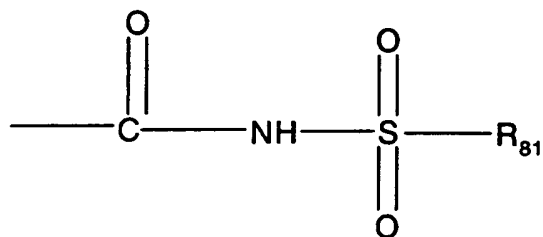
The term, "(acidic group)" means an organic group which when attached to an indole nucleus at position 5, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

-5-tetrazolyl,

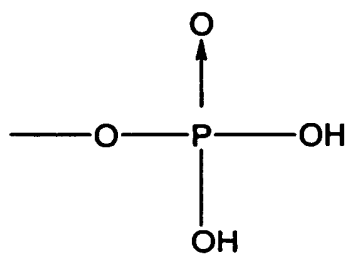
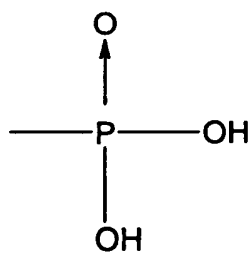
-SO<sub>3</sub>H,

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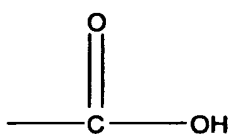
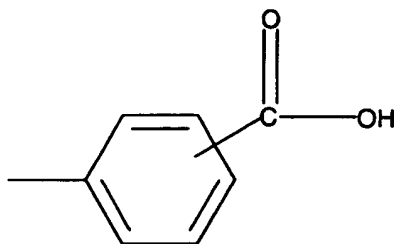
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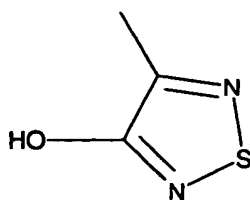
5



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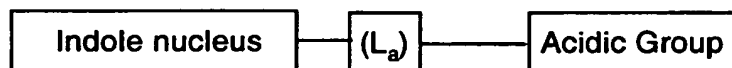


or



where n is 1 to 8, R<sub>80</sub> is a metal or C<sub>1</sub>-C<sub>8</sub> and R<sub>81</sub>  
 5 is an organic substituent or -CF<sub>3</sub>.

The words, "acid linker" refer to a divalent  
 linking group symbolized as, -(L<sub>a</sub>)-, which has the  
 function of joining the 5 position of the indole nucleus  
 10 to an acidic group in the general relationship:

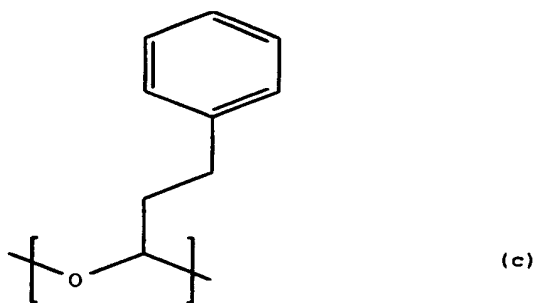
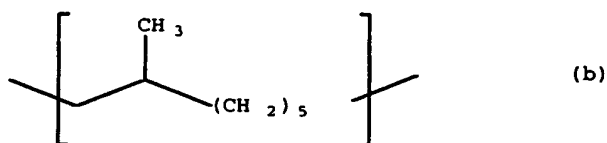
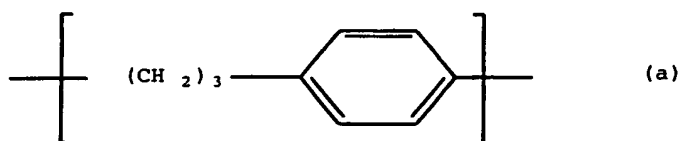


The words, "acid linker length", refer to the number  
 of atoms (excluding hydrogen) in the shortest chain of the  
 15 linking group -(L<sub>a</sub>)- that connects the 5 position of the

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indole nucleus with the acidic group. The presence of a carbocyclic ring in  $-(L_A)-$  counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in  
5 the acid linker counts as 2 atoms in calculating the length of  $-(L_A)-$ . Illustrative acid linker groups are;



10 wherein, groups (a), (b), and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "amine", includes primary, secondary and tertiary amines.

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The terms, "mammal" and "mammalian" include human and domesticated quadrupeds.

The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals,  $-\text{CH}_2-\text{CH}_2-$  and  $-\text{CH}_2-$ .

5

The term, "group containing 1 to 4 non-hydrogen atoms" refers to relatively small groups which form substituents at the 2 position of the indole nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as  $-\text{CF}_3$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{SO}_3$ ; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as  $-\text{CH}_3$ ,  $-\text{C}_2\text{H}_5$ , and  $-\text{CH}=\text{CH}_2$ .

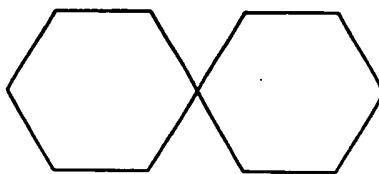
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The term "oxime amide" means the radical,  
 $-\text{C}=\text{NOR}-\text{C}(\text{O})\text{NH}_2$

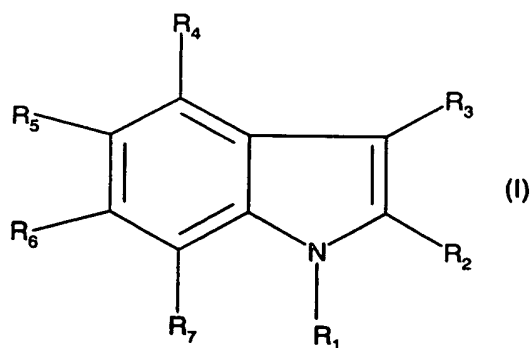
The term "thio-oxime amide" means the radical  
 $-\text{C}=\text{NOR}-\text{C}(\text{S})-\text{NH}_2$ .

The term "spiro[5.5]undecanyl" refers to the group represented by the formula;

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**II. The amino acid 1H-indole Compounds of the Invention:**

The present invention provides novel classes of  
5 indole compounds useful as sPLA2 inhibitors for the  
treatment of inflammation. Classes of indole compounds  
of this invention include indole glyoxylamide amino acid  
derivatives, indole-3-oxime amide amino acid derivatives  
and indole acetamide amino acid derivatives. The  
10 compounds of the invention have the general formula (I)  
or a pharmaceutically acceptable salt, solvate or  
prodrug thereof;



15

wherein ;

R<sub>1</sub> is selected from groups (a), (b), and (c)

wherein;



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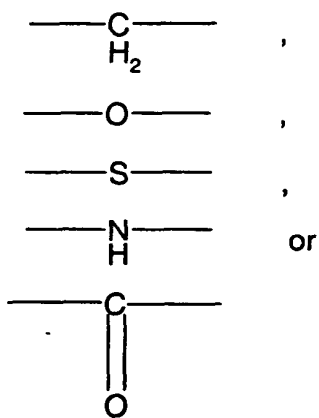
(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or  
5 more independently selected non-interfering substituents; or

(c) is the group  $-(L_1)-R_{11}$ ; where,  $-(L_1)-$  is a divalent linking group of 1 to 8 atoms and where  $R_{11}$  is a group selected from (a) or (b);

10  $R_2$  is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

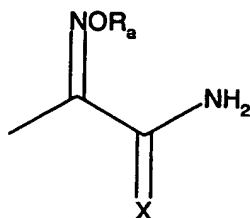
$R_3$  is  $-(L_3)-Z$ , where  $-(L_3)-$  is a divalent linker group selected from a bond or a divalent group selected from:



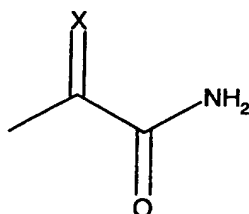
15

and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,

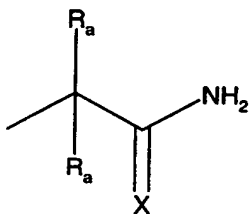
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or



or



5

wherein X is oxygen or sulfur,  $R_a$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, aralkyl and -CN;

$R_4$  is the group,  $-(L_C)-(acylamino\ acid\ group)$ ;

10 wherein  $-(L_C)-$ , is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

$R_5$  is selected from hydrogen, a non-interfering substituent, or the group,  $-(L_A)-(acidic\ group)$ ; wherein  $-(L_A)-$ , is an acid linker having an acid linker length

15 of 1 to 8.

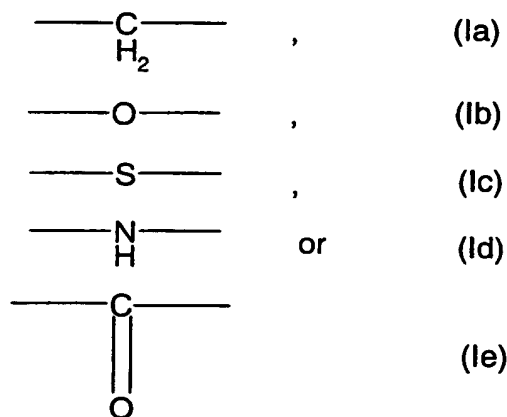
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R<sub>6</sub> and R<sub>7</sub> are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

**Preferred Subgroups of Compounds of Formula (I):**  
**Preferred R<sub>1</sub> substituents:**

A preferred subclass of compounds of formula (I) are those where for R<sub>1</sub> the divalent linking group -(L<sub>1</sub>)- is a group represented by any one of the following formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):

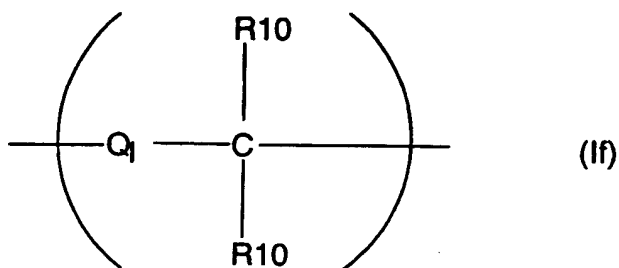


15

or

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where  $\text{Q}_1$  is a bond or any of the divalent groups (Ia),  
 (Ib), (Ic), (Id), (Ie), and (If) and each  $\text{R}_{10}$  is  
 5 independently hydrogen,  $\text{C}_{1-8}$  alkyl,  $\text{C}_{1-8}$  haloalkyl or  
 $\text{C}_{1-8}$  alkoxy.

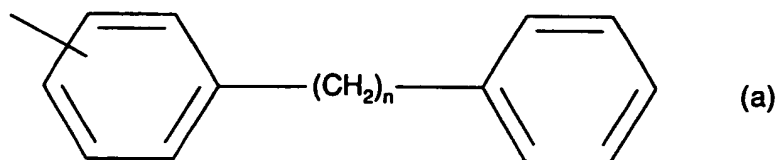
Particularly preferred as the linking group  $-(\text{L}_1)-$  of  
 $\text{R}_1$  is an alkylene chain of 1 or 2 carbon atoms, namely,  
 10  $-(\text{CH}_2)-$  or  $-(\text{CH}_2-\text{CH}_2)-$ .

The preferred group for  $\text{R}_{11}$  is a substituted or  
 unsubstituted group selected from the group consisting of  
 $\text{C}_5\text{-C}_{14}$  cycloalkyl,  $\text{C}_5\text{-C}_{14}$  cycloalkenyl, phenyl, naphthyl,  
 15 norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,  
 indenyl, stilbenyl, terphenyl, diphenylethylenyl,  
 phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,  
 biphenyl, bibenzyl and related bibenzyl homologues  
 represented by the formula (a);

20

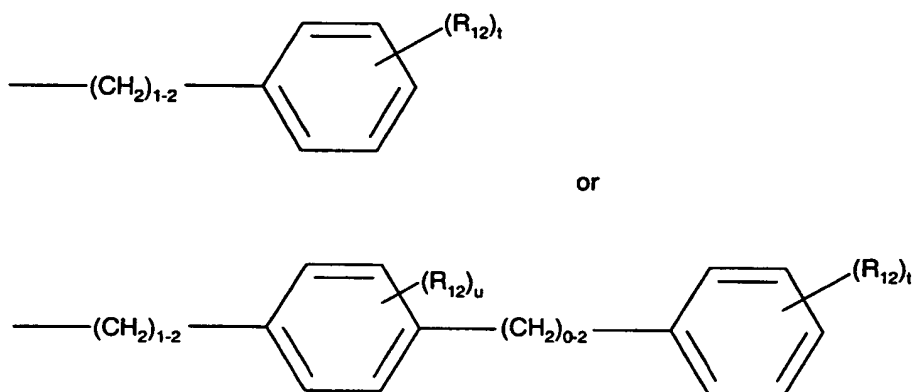
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where n is a number from 1 to 8.

Particularly preferred are compounds wherein for  $R_1$   
 5 the combined group  $-(L_1)-R_{11}$  is selected from the group  
 consisting of

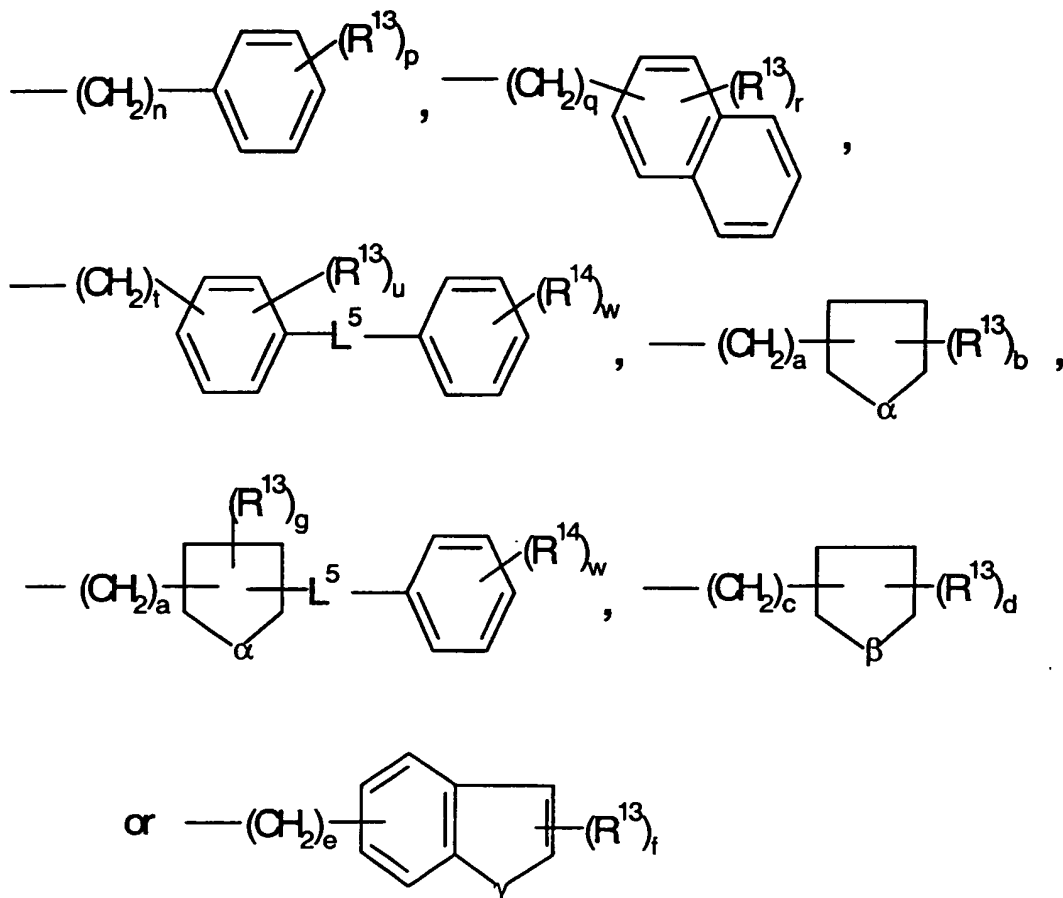


where  $R_{12}$  is a radical independently selected from halo,  
 $C_1-C_8$  alkyl,  $C_1-C_8$  alkoxy,  $-S-(C_1-C_8 \text{ alkyl})$ ,  $-O-(C_1-C_8$   
 10  $\text{alkyl})$  and  $C_1-C_8$  haloalkyl where t is a number from 0 to  
 5 and u is a number from 0 to 4 is the group  $-(L_1)-R_{11}$ ;  
 where,  $-(L_1)-$  is a divalent linking group of 1 to 8  
 atoms and where  $R_{11}$  is a group selected from (a) or (b).

15 Preferred for  $R_{11}$  is  $-(CH_2)_m-R^{12}$  wherein m is an  
 integer from 1 to 6, and  $R^{12}$  is (d) a group represented by  
 the formula:

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wherein a, c, e, n, q, and t are independently an integer from 0 to 2,  $R^{13}$  and  $R^{14}$  are independently selected from a halogen,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$

5 alkyloxy,  $C_1$  to  $C_8$  alkylthio, aryl, heteroaryl, and  $C_1$  to  $C_8$  haloalkyl,  $\alpha$  is an oxygen atom or a sulfur atom,  $L^5$  is a bond,  $-(CH_2)_v-$ ,

$-C=C-$ ,  $-CC-$ ,  $-O-$ , or  $-S-$ , v is an integer from 0 to 2,  $\beta$  is  $-CH_2-$  or  $-(CH_2)_2-$ ,  $\gamma$  is an oxygen atom or a sulfur

10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer

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from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C<sub>1</sub> to C<sub>6</sub> alkyl, C<sub>1</sub> to C<sub>8</sub> alkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyl, aryl, and a halogen.

5

**Preferred R<sub>2</sub> substituents:**

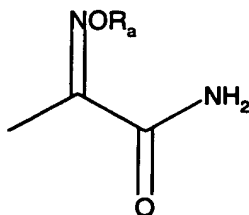
R<sub>2</sub> is preferably selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, -O-(C<sub>1</sub>-C<sub>3</sub> alkyl),

10 -S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>3</sub>-C<sub>4</sub> cycloalkyl -CF<sub>3</sub>, halo, -NO<sub>2</sub>, -CN, -SO<sub>3</sub>. Particularly preferred R<sub>2</sub> groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF<sub>3</sub>, -Cl, -Br, or -O-CH<sub>3</sub>.

15 **Preferred R<sub>3</sub> substituents:**

A preferred subclass of compounds of formula (I) are those wherein X is oxygen.

Another preferred subclass of compounds of  
20 formula (I) are those wherein Z is an oxime amide group.



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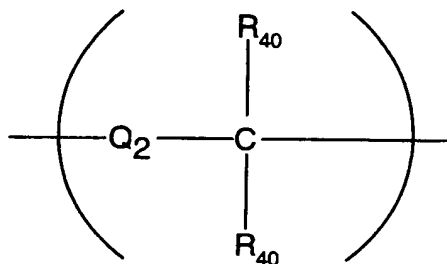
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Also preferred are compounds of formula (I) wherein  $R_3$  is an oxime amide group and  $R_a$  is hydrogen, methyl or ethyl. For the group  $R_3$  it is preferred that the linking group  $-(L_3)-$  be a bond.

5

**Preferred  $R_4$  substituents:**

Another preferred subclass of compounds of formula (I) are those wherein  $R_4$  is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group,  $-(L_C)-$ , for  $R_4$  is selected from a group represented by the formula;

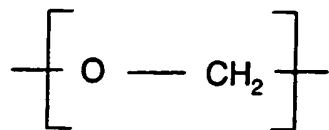


where  $Q_2$  is selected from the group  $-(CH_2)-$ ,  $-O-$ ,  $-NH-$ ,  $-C(O)-$ , and  $-S-$ , and each  $R_{40}$  is independently selected from hydrogen,  $C_1$ - $C_8$  alkyl, aryl,  $C_1$ - $C_8$  alkaryl,  $C_1$ - $C_8$  alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker,  $-(L_C)-$ , for  $R_4$  is selected from the specific groups;

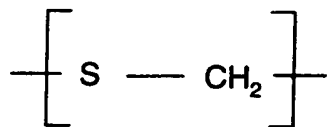
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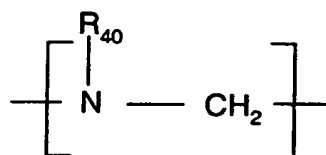
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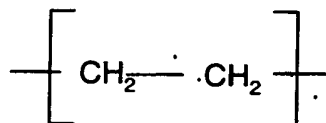
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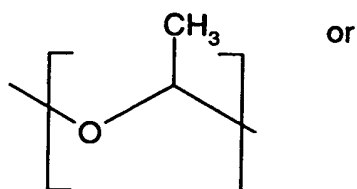
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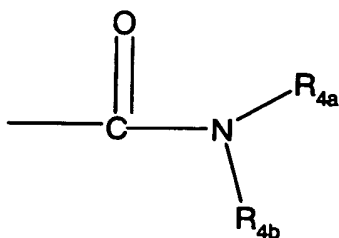


,

where  $\text{R}_{40}$  is hydrogen or  $\text{C}_1$  -  $\text{C}_8$  alkyl.

Preferred as the (acylamino acid group) in the group  $\text{R}_4$

5 is the group:



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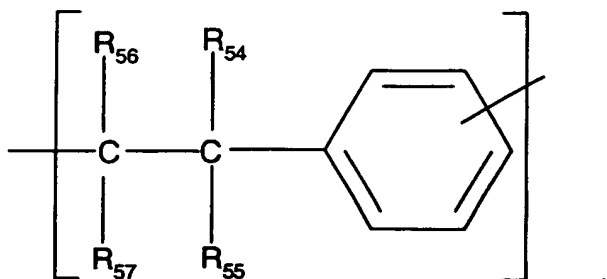
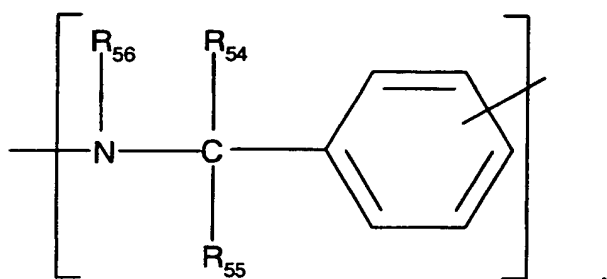
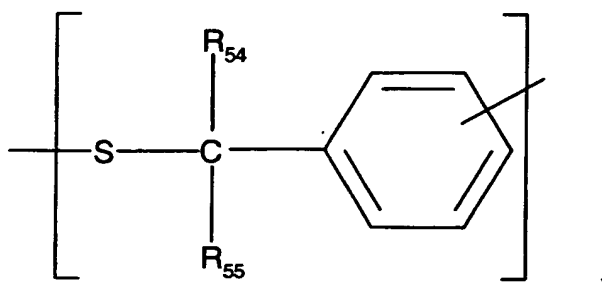
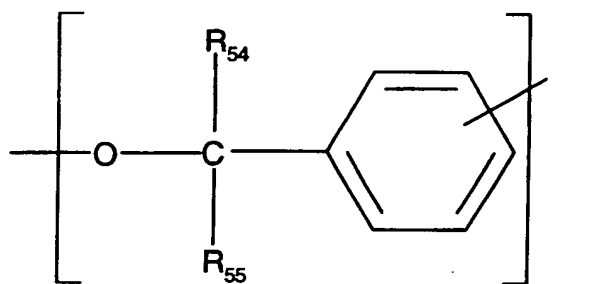
wherein R<sup>4a</sup> is selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl; and wherein NR<sup>4b</sup> is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R<sup>4a</sup> group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and derivatives thereof. A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

Particularly preferred are R<sup>4b</sup> groups that combine with the nitrogen atom to represent amino acid residues from the amino acid groups selected from: glycine, glycine methyl ester, L-alanine, L-alanine methylester, L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl ester, L-phenyl alanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L-valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.

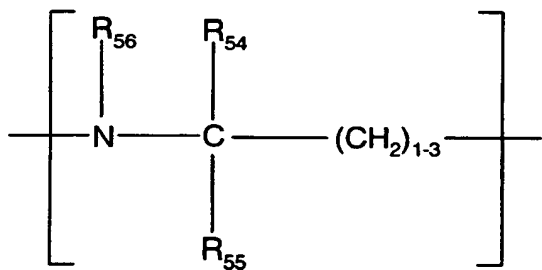
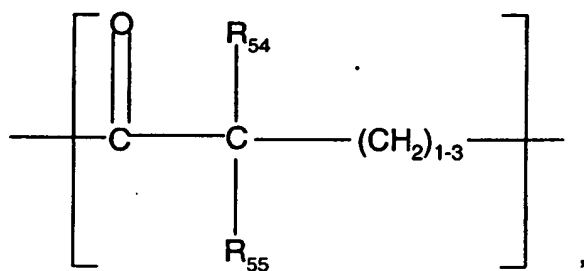
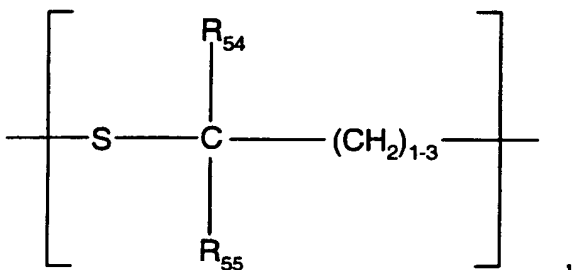
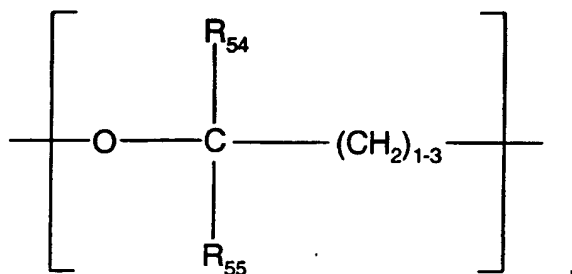
**Preferred R<sub>5</sub> Substituents:**

Preferred acid linker, -(L<sub>a</sub>)-, for R<sub>5</sub> is selected from the group consisting of;

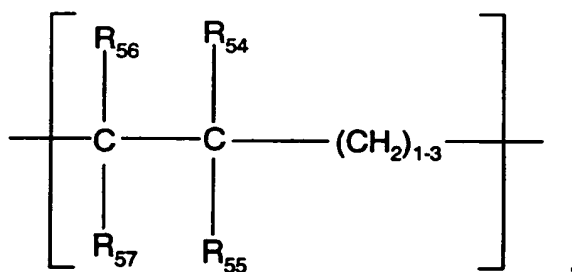
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and



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wherein R<sub>54</sub>, R<sub>55</sub>, R<sub>56</sub> and R<sub>57</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, or halo. Preferred (acidic group) for R<sub>5</sub> is selected from the group consisting of -CO<sub>2</sub>H, -SO<sub>3</sub>H and

5 -P(O)(OH)<sub>2</sub>.

**Preferred R<sub>6</sub> and R<sub>7</sub> substituents:**

Another preferred subclass of compounds of formula (I) are those wherein for R<sub>6</sub> and R<sub>7</sub> the non-

10 interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C<sub>4</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>7</sub>-C<sub>12</sub> aralkyl, C<sub>7</sub>-C<sub>12</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub>

15 alkenyloxy, C<sub>2</sub>-C<sub>6</sub> alkynyloxy, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyloxy, C<sub>2</sub>-C<sub>12</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>12</sub> alkylcarbonylamino, C<sub>2</sub>-C<sub>12</sub> alkoxyamino, C<sub>2</sub>-C<sub>12</sub> alkoxyaminocarbonyl, C<sub>1</sub>-C<sub>12</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>2</sub>-C<sub>12</sub> alkylthiocarbonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>

20 alkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, -C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH<sub>2</sub>)<sub>n</sub>-CO<sub>2</sub>H,

25 chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,

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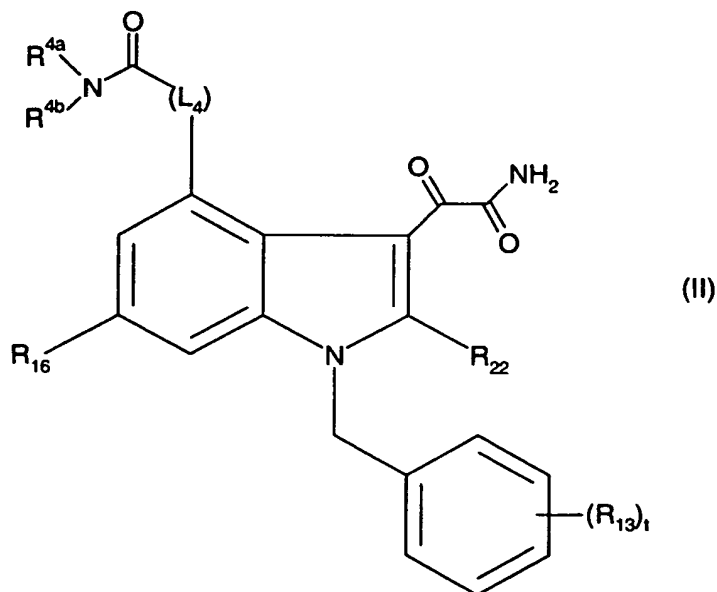
-30-

iodo, nitro, phosphono,  $-\text{SO}_3\text{H}$ , thioacetal, thiocarbonyl, and carbonyl; where  $n$  is from 1 to 8.

Most preferred as non-interfering substituents are  
5 methyl, ethyl, propyl, and isopropyl.

Preferred compounds of the invention are those having the general formula (II), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof;

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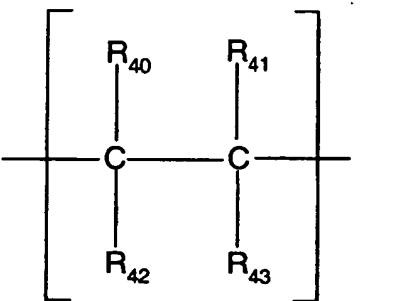
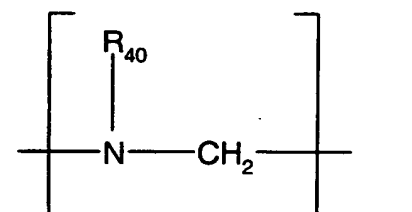
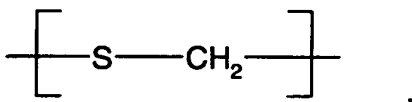
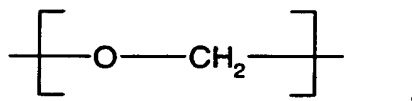
wherein ;

15  $\text{R}_{22}$  is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl,  $-\text{F}$ ,  $-\text{CF}_3$ ,  $-\text{Cl}$ ,  $-\text{Br}$ , or  $-\text{O}-\text{CH}_3$ ;

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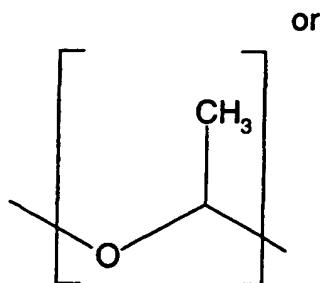
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wherein  $R^{4a}$  is selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl; and wherein  $NR^{4b}$  is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred  $R^{4a}$  group is the group hydrogen (H); and - (L<sub>4</sub>)- is a divalent group selected from;



10

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where R<sub>40</sub>, R<sub>41</sub>, R<sub>42</sub>, and R<sub>43</sub> are each independently selected from hydrogen or C<sub>1</sub>-C<sub>8</sub> alkyl.

R<sub>16</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>8</sub> alkylthio C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, and halo.

R<sub>13</sub> is selected from hydrogen and C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>8</sub> alkyl), C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> phenyl, halophenyl, hydroxyalkyl, and halo, and t is an integer from 0 to 5.

Preferred specific compounds (and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof) which are illustrative of the compounds of the invention are as follow:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;



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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]glycine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-alanine;

5        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-alanine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
10 1H-indol-4-yl]oxy]acetyl]-L-leucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-leucine;

15        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
20 1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

5        [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

10       [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

15       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

20       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

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The salts of the above indole compounds represented by formulae (I) and (II) are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups  
5 various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium,  
10 magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

15 Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous  
20 bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable  
25 organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate,

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bitartrate, borate, bromide, camsylate, carbonate,  
chloride, clavulanate, citrate, chloride, edetate,  
edisylate, estolate, esylate, fluoride, fumarate,  
gluceptate, gluconate, glutamate, glycolylarsanilate,  
5 hexylresorcinate, bromide, chloride, hydroxynaphthoate,  
iodide, isothionate, lactate, lactobionate, laurate,  
malate, malseate, mandelate, mesylate, methylbromide,  
methylnitrate, methylsulfate, mucate, napsylate, nitrate,  
oleate, oxalate, palmitate, pantothenate, phosphate,  
10 polygalacturonate, salicylate, stearate, subacetate,  
succinate, tannate, tartrate, tosylate, trifluoroacetate,  
trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or  
15 more chiral centers and may thus exist in optically active  
forms. Likewise, when the compounds contain an alkenyl or  
alkenylene group there exists the possibility of cis- and  
trans- isomeric forms of the compounds. The R- and S-  
isomers and mixtures thereof, including racemic mixtures  
20 as well as mixtures of cis- and trans- isomers, are  
contemplated by this invention. Additional asymmetric  
carbon atoms can be present in a substituent group such as  
an alkyl group. All such isomers as well as the mixtures  
thereof are intended to be included in the invention. If  
25 a particular stereoisomer is desired, it can be prepared  
by methods well known in the art by using stereospecific

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reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods.

5 For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can

10 be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable

15 groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative

20 form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid

25 derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides

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prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

10

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

15

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

20

a) The 1H-indole-3-glyoxylamide amino derivative compounds of the invention are prepared by room temperature base catalyzed condensation of the amino acid protected at the acid terminus by protecting group

25

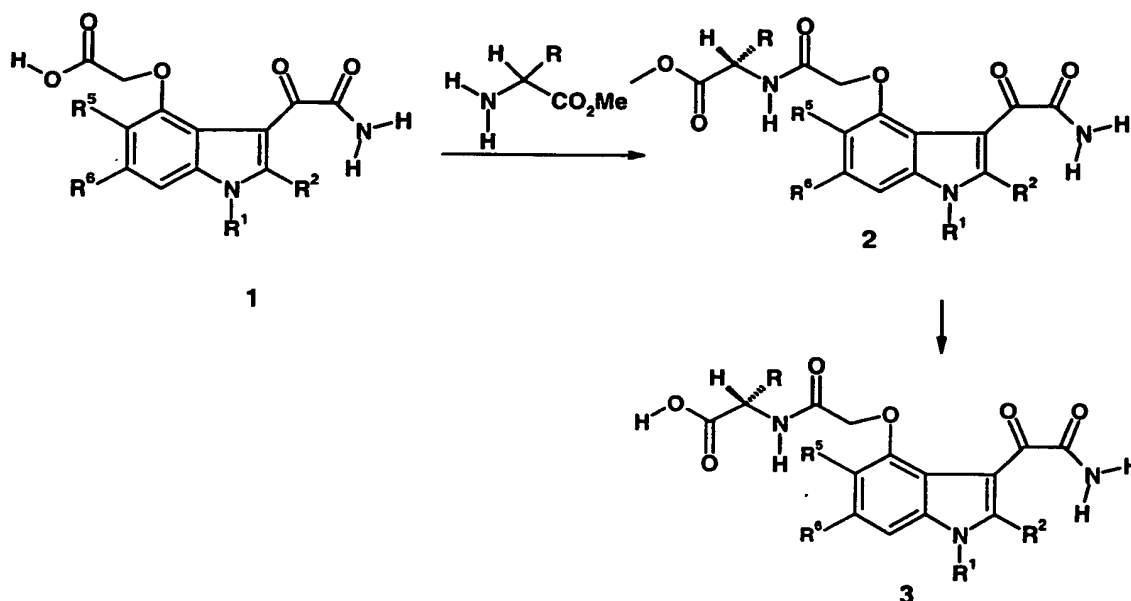
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known in the literature but preferably as the methyl ester with the 1H-indole-3-glyoxylamide acid derivative compound of formula (1) as shown in Scheme I:

5

Scheme 1



Typically, the condensation or coupling is performed in a solvent such a dimethyl formamide, tetrahydrofuran or aqueous mixtures of the like. In general protic solvents are preferred for the purpose of this invention. The reaction is catalyzed by a base including weak organic or inorganic bases. Organic bases such as collidine are preferred. The reaction is also preferably run in the presence of agents that retard or reduce racemization of the amino acid or its

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derivative, such as for example, benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate.

Upon completion of the reaction, the mixture is concentrated in vacuo. The resulting product mixture is  
5 chromatographed to obtain the target compound.

One of skill in the art is aware that the derivatives of the acid such as the acid salt or the methyl ester of the acid, can be reacted with the amino acid or  
10 derivatives thereof to obtain the protected compound 2 or a corresponding derivative. Such methods are well known in the arts and can be found in reference texts such as for example J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C.  
15 Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989. The protected compounds of formula (2) are also useful sPLA<sub>2</sub> inhibitors and are also compounds of this invention.

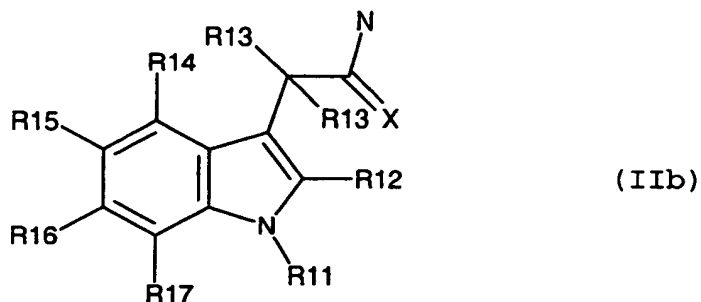
20        b)        1H-indole-3-acetamide amino acid derivative sPLA<sub>2</sub> inhibitors are similarly prepared by condensation of the protected amino acid with the 1H-indole-3-acetamide sPLA<sub>2</sub> inhibitor. The 1H-indole-3-acetamide sPLA<sub>2</sub> inhibitors and methods of making them are set out in U.S.  
25 Patent No. 5,684,034, the entire disclosure of which is incorporated herein by reference. Indole-3-acetamide



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amino acid derivative sPLA2 inhibitors of this invention are represented by compounds of formula (IIb), and pharmaceutically acceptable salts and prodrug derivatives thereof,



5

wherein ;

X is oxygen or sulfur;

R<sub>11</sub> is selected from groups (i), (ii) (iii) and (iv)

10 where;

(i) is C<sub>6</sub>-C<sub>20</sub> alkyl, C<sub>6</sub>-C<sub>20</sub> alkenyl, C<sub>6</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>20</sub> haloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkyl, or

(ii) is aryl or aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkylthio, C<sub>1</sub>-

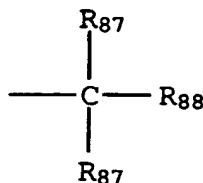
15 C<sub>10</sub> alkoxyl, carboxyl, amino, or hydroxyamino; or

(iii) is -(CH<sub>2</sub>)<sub>n</sub>-(R<sub>80</sub>), or -(NH)-(R<sub>81</sub>), where n is 1 to 8, and R<sub>80</sub> is a group recited in (i), and R<sub>81</sub> is selected from a group recited in (i) or (ii);

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(iv) is



- where R<sub>87</sub> is hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl, and R<sub>88</sub> is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C<sub>1</sub>-C<sub>10</sub> alkylthio, C<sub>1</sub>-C<sub>10</sub> alkoxy, phenyl, nitro, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;
- 10 R<sub>12</sub> is halo, C<sub>1</sub>-C<sub>2</sub> alkylthio, C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkyaryl or C<sub>1</sub>-C<sub>2</sub> alkoxy;
- each R<sub>13</sub> is independently hydrogen, halo, or methyl;
- R<sup>14</sup> is the group -L<sub>C</sub>-[acylamino acid], wherein the acylamino acid group is -C(O)-NR<sup>14a</sup>R<sup>14b</sup> wherein R<sup>14a</sup> is
- 15 selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl; and -L<sub>C</sub>- is as defined *supra*, and wherein NR<sup>14b</sup> is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. Most
- 20 preferred are compounds of formula II wherein the group R<sup>14a</sup> is a hydrogen atom (H). A preferred source of the amino acid residue NR<sup>14b</sup> is an amino acid selected from the group comprising isoleucine, valine, phenylalanine,

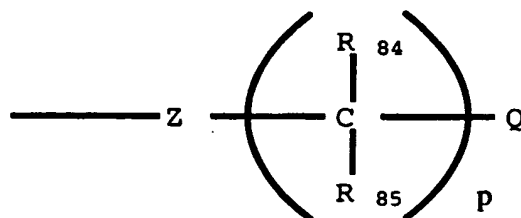
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aspartic acid, leucine, glycine and isomers and derivatives thereof,

$R_{15}$  is selected from hydrogen, a non-interfering substituent, or the group,  $-(L_a)-(acidic\ group)$ ; wherein  
 5  $-(L_a)-$ , is an acid linker having an acid linker length of 1 to 8;

$R_{16}$  and  $R_{17}$  are each independently hydrogen,  $C_1-C_{10}$  alkyl,  $C_1-C_{10}$  alkenyl,  $C_1-C_{10}$  alkynyl,  $C_3-C_8$  cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in  
 10 the set  $R_{15}$ ,  $R_{16}$ , and  $R_{17}$ , combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or  $C_1-C_{10}$  haloalkyl,  $C_1-C_{10}$  alkoxy,  $C_1-C_{10}$  haloalkoxy,  $C_4-C_8$  cycloalkoxy, phenoxy, halo, hydroxy, carboxyl,  $-SH$ ,  $-CN$ ,  
 15  $C_1-C_{10}$  alkylthio, arylthio, thioacetal,  $-C(O)O(C_1-C_{10} alkyl)$ , hydrazide, hydrazino, hydrazido,  $-NH_2$ ,  $-NO_2$ ,  $-NR_{82}R_{83}$ , and  $-C(O)NR_{82}R_{83}$ , where,  $R_{82}$  and  $R_{83}$  are independently hydrogen,  $C_1-C_{10}$  alkyl,  $C_1-C_{10}$  hydroxyalkyl, or taken together with N,  $R_{82}$  and  $R_{83}$  form a 5- to 8-  
 20 membered heterocyclic ring; or a group having the formula;



where,

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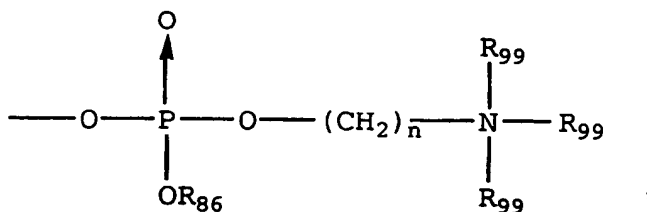
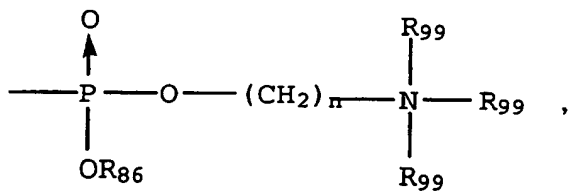
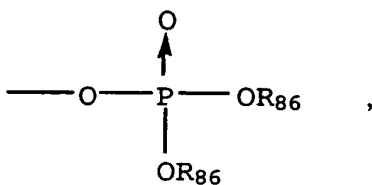
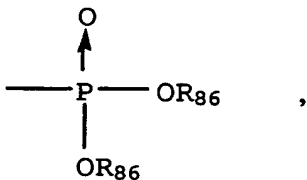
R<sub>84</sub> and R<sub>85</sub> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, hydroxy, or R<sub>84</sub> and R<sub>85</sub> taken together are =O;

p is 1 to 5,

5 Z is a bond, -O-, -N(C<sub>1</sub>-C<sub>10</sub> alkyl)-, -NH-, or -S-;

and

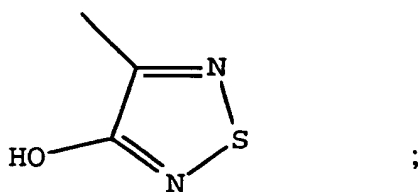
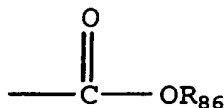
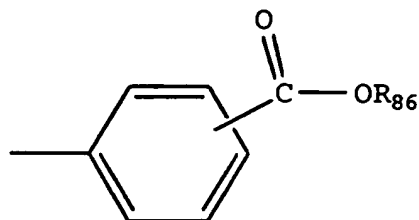
Q is -CON(R<sub>82</sub>R<sub>83</sub>), -5-tetrazolyl, -SO<sub>3</sub>H,



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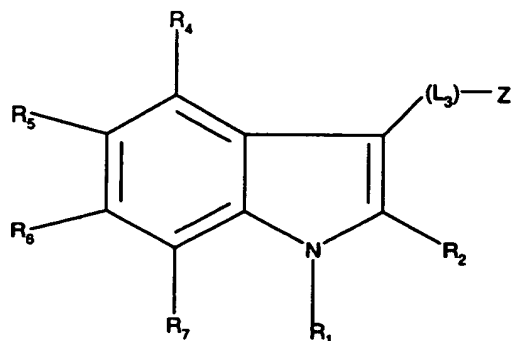
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where n is 1 to 8, R<sub>86</sub> is independently selected from  
hydrogen, a metal, or C<sub>1</sub>-C<sub>10</sub> alkyl, and R<sub>99</sub> is selected  
5 from hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl.

c) Indole-3-Oxime amide compounds of the invention  
are represented by compounds of formula (III) or a  
pharmaceutically acceptable salt, solvate or prodrug  
10 thereof;



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wherein ;

$R_1$  is selected from groups (a), (b), and (c)

wherein;

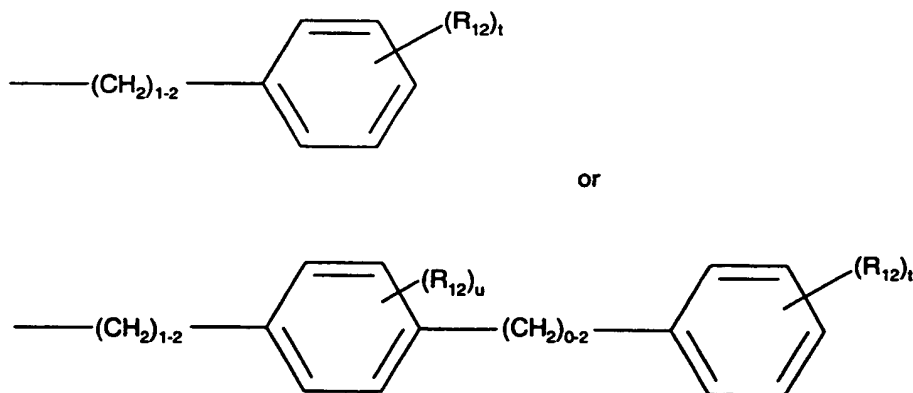
5 (a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or more independently selected non-interfering

10 substituents; or

(c) is the group  $-(L_1)-R_{11}$ ; where,  $-(L_1)-$  is a divalent linking group of 1 to 8 atoms and where  $R_{11}$  is a group selected from (a) or (b).

15 Particularly preferred are compounds wherein for  $R_1$  the combined group  $-(L_1)-R_{11}$  is selected from the group consisting of

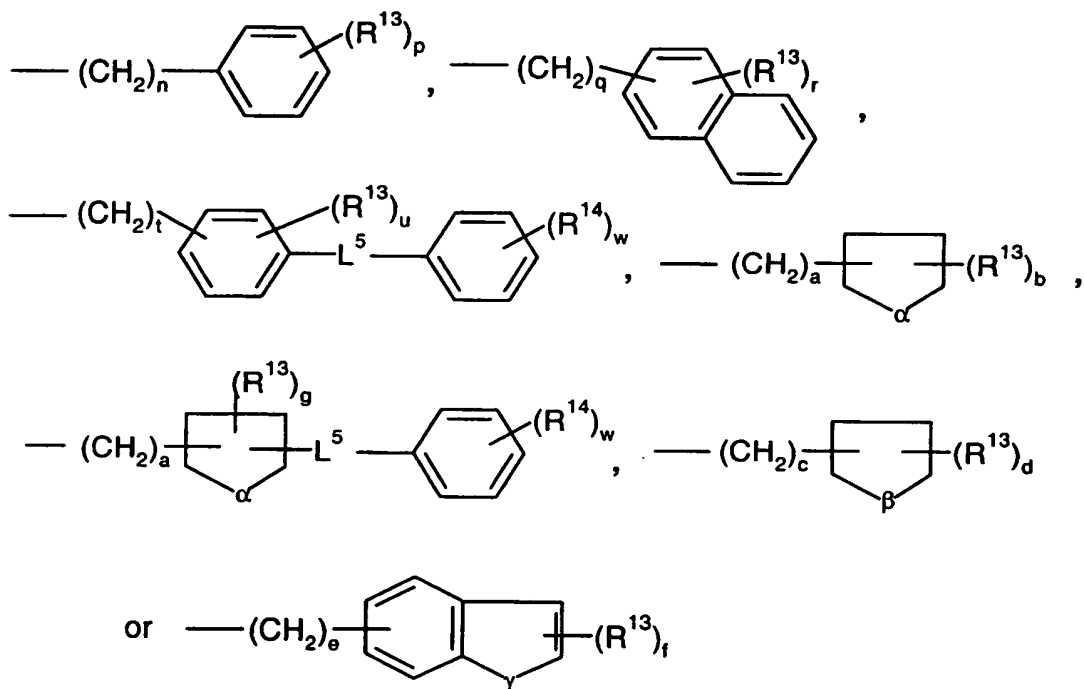


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where  $R_{12}$  is a radical independently selected from halo,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  alkoxy,  $-S-(C_1-C_8 \text{ alkyl})$ ,  $-O-(C_1-C_8 \text{ alkyl})$  and  $C_1$ - $C_8$  haloalkyl where  $t$  is a number from 0 to 5 and  $u$  is a number from 0 to 4.

5

Also preferred for  $R_{11}$  is  $-(CH_2)_m-R^{12}$  wherein  $m$  is an integer from 1 to 6, and  $R^{12}$  is (d) a group represented by the formula:



10

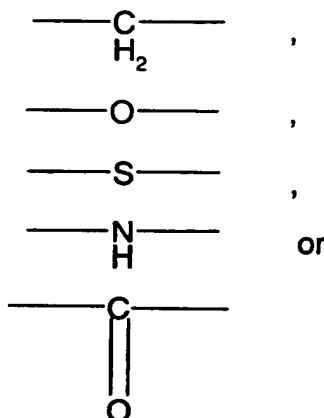
wherein  $a$ ,  $c$ ,  $e$ ,  $n$ ,  $q$ , and  $t$  are independently an integer from 0 to 2,  $R^{13}$  and  $R^{14}$  are independently selected from a halogen,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$  alkyloxy,  $C_1$  to  $C_8$  alkylthio, aryl, heteroaryl, and  $C_1$  to

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$C_8$  haloalkyl,  $\alpha$  is an oxygen atom or a sulfur atom,  $L^5$  is a bond,  $-(CH_2)_v-$ ,  $-C=C-$ ,  $-CC-$ ,  $-O-$ , or  $-S-$ ,  $v$  is an integer from 0 to 2,  $\beta$  is  $-CH_2-$  or  $-(CH_2)_2-$ ,  $\gamma$  is an oxygen atom or a sulfur atom,  $b$  is an integer from 0 to 3,  $d$  is an integer from 0 to 4,  $f$ ,  $p$ , and  $w$  are independently an integer from 0 to 5,  $r$  is an integer from 0 to 7, and  $u$  is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of  $C_1$  to  $C_6$  alkyl,  $C_1$  to  $C_8$  alkyloxy,  $C_1$  to  $C_8$  haloalkyloxy,  $C_1$  to  $C_8$  haloalkyl, aryl, and a halogen.

$R_2$  is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

$-(L_3)-Z$ , is the group where  $-(L_3)-$  is a divalent linker group selected from a bond or a divalent group selected from:

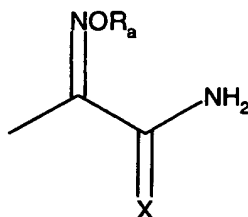




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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,



5

wherein, X is oxygen or sulfur; and  $R_a$  is selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, aralkyl and -CN;

10  $R_4$  is the group,  $-(L_C)-(acylamino\ acid\ group)$ ; wherein  $-(L_C)-$ , is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

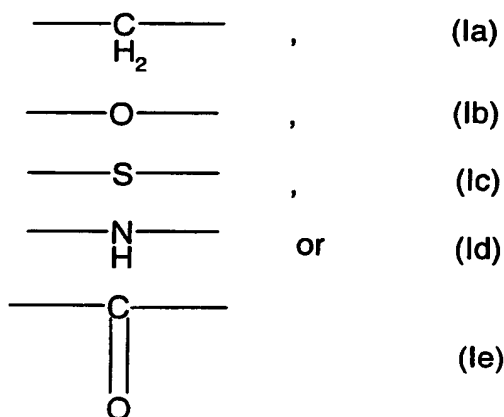
$R_5$  is selected from hydrogen, a non-interfering substituent, or the group,  $-(L_A)-(acidic\ group)$ ; wherein  
15  $-(L_A)-$ , is an acid linker having an acid linker length of 1 to 8.

$R_6$  and  $R_7$  are selected from hydrogen, non-interfering substituent, carbocyclic radical,  
20 carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

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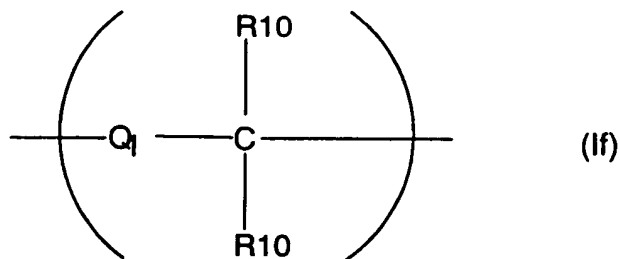
**Preferred Subgroups of Compounds of Formula (III):**  
**Preferred R<sub>1</sub> substituents:**

A preferred subclass of compounds of formula (III)  
 5 are those where for R<sub>1</sub> the divalent linking group -(L<sub>1</sub>)-  
 is a group represented by any one of the following  
 formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



10

or



15 where Q<sub>1</sub> is a bond or any of the divalent groups (Ia),  
 (Ib), (Ic), (Id), (Ie), and (If) and each R<sub>10</sub> is

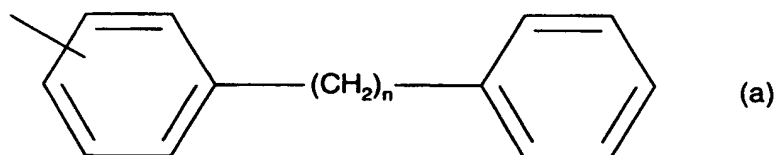
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independently hydrogen, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl or C<sub>1-8</sub> alkoxy.

Particularly preferred as the linking group -(L<sub>1</sub>)- of  
5 R<sub>1</sub> is an alkylene chain of 1 or 2 carbon atoms, namely,  
-(CH<sub>2</sub>)- or -(CH<sub>2</sub>-CH<sub>2</sub>)-.

The preferred group for R<sub>11</sub> is a substituted or  
unsubstituted group selected from the group consisting of  
10 C<sub>5</sub>-C<sub>14</sub> cycloalkyl, C<sub>5</sub>-C<sub>14</sub> cycloalkenyl, phenyl, naphthyl,  
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,  
indenyl, stilbenyl, terphenyl, diphenylethylenyl,  
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,  
biphenyl, bibenzylyl and related bibenzylyl homologues  
15 represented by the formula (a);

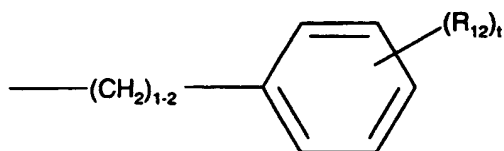


where n is a number from 1 to 8.

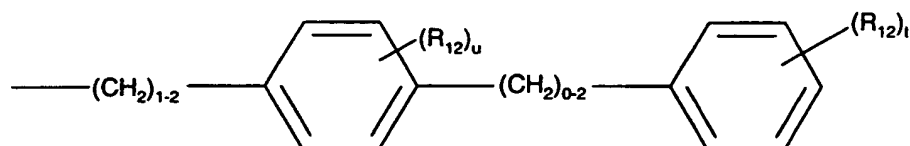
20 Particularly preferred are compounds wherein for R<sub>1</sub>  
the combined group -(L<sub>1</sub>)-R<sub>11</sub> is selected from the group  
consisting of

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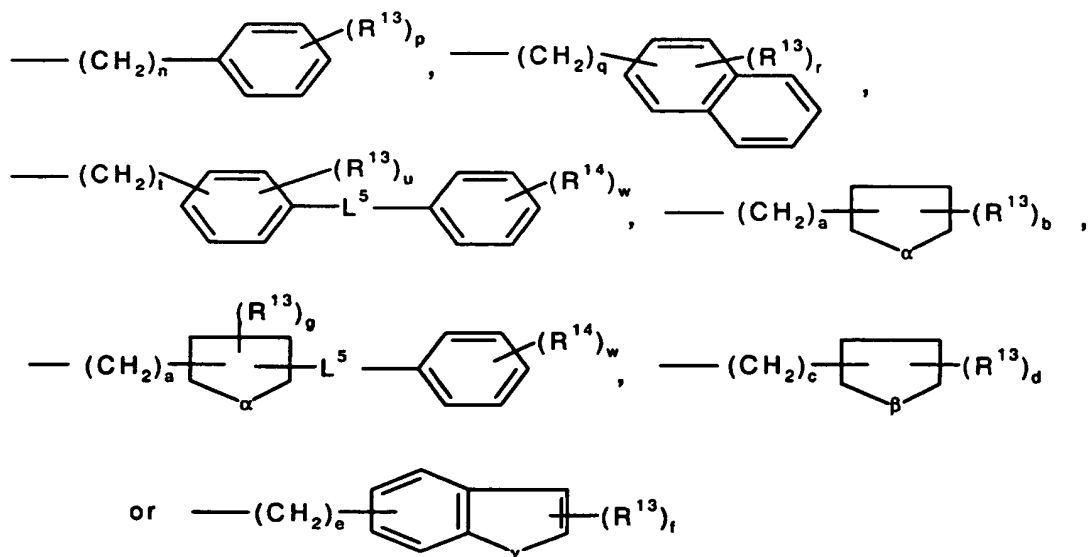


or



where  $\text{R}_{12}$  is a radical independently selected from halo,  $\text{C}_1\text{-C}_8$  alkyl,  $\text{C}_1\text{-C}_8$  alkoxy,  $-\text{S}-(\text{C}_1\text{-C}_8 \text{ alkyl})$ ,  $-\text{O}-(\text{C}_1\text{-C}_8$   
 5 alkyl) and  $\text{C}_1\text{-C}_8$  haloalkyl where  $t$  is a number from 0 to 5 and  $u$  is a number from 0 to 4.

Also preferred for  $\text{R}_{11}$  is  $-(\text{CH}_2)_m\text{-R}^{12}$  wherein  $m$  is an  
 integer from 1 to 6, and  $\text{R}^{12}$  is (d) a group represented by  
 10 the formula:



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wherein a, c, e, n, q, and t are independently an integer from 0 to 2,  $R^{13}$  and  $R^{14}$  are independently selected from a halogen,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$  alkyloxy,  $C_1$  to  $C_8$  alkylthio, aryl, heteroaryl, and  $C_1$  to  $C_8$  haloalkyl,  $\alpha$  is an oxygen atom or a sulfur atom,  $L^5$  is a bond,  $-(CH_2)_v-$ ,  $-C=C-$ ,  $-CC-$ ,  $-O-$ , or  $-S-$ , v is an integer from 0 to 2,  $\beta$  is  $-CH_2-$  or  $-(CH_2)_2-$ ,  $\gamma$  is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of  $C_1$  to  $C_6$  alkyl,  $C_1$  to  $C_8$  alkyloxy,  $C_1$  to  $C_8$  haloalkyloxy,  $C_1$  to  $C_8$  haloalkyl, aryl, and a halogen.

**Preferred  $R_2$  substituents:**

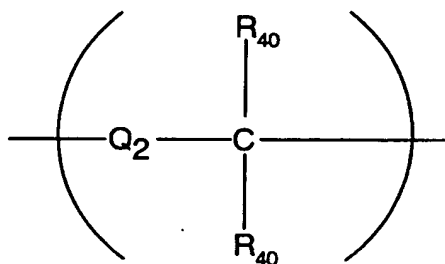
$R_2$  is preferably selected from the group consisting of hydrogen,  $C_1$ - $C_4$  alkyl,  $C_2$ - $C_4$  alkenyl,  $-O-(C_1$ - $C_3$  alkyl),  $-S-(C_1$ - $C_3$  alkyl),  $-C_3$ - $C_4$  cycloalkyl  $-CF_3$ , halo,  $-NO_2$ ,  $-CN$ ,  $-SO_3$ . Particularly preferred  $R_2$  groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl,  $-F$ ,  $-CF_3$ ,  $-Cl$ ,  $-Br$ , or  $-O-CH_3$ .

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**Preferred  $R_4$  substituents:**

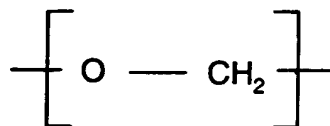
Another preferred subclass of compounds of formula (III) are those wherein  $R_4$  is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group,  $-(L_C)-$ , for  $R_4$  is selected from a group represented by the formula;



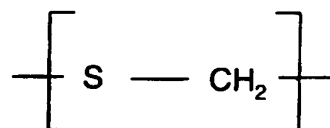
10

where  $Q_2$  is selected from the group  $-(CH_2)-$ ,  $-O-$ ,  $-NH-$ ,  $-C(O)-$ , and  $-S-$ , and each  $R_{40}$  is independently selected from hydrogen,  $C_1$ - $C_8$  alkyl, aryl,  $C_1$ - $C_8$  alkaryl,  $C_1$ - $C_8$  alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker,  $-(L_C)-$ , for  $R_4$  is selected from the specific groups;

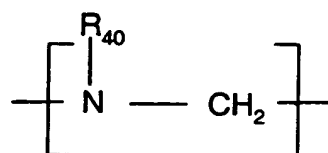
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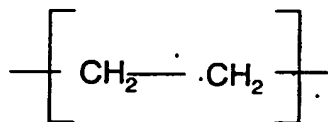
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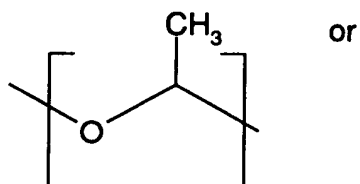
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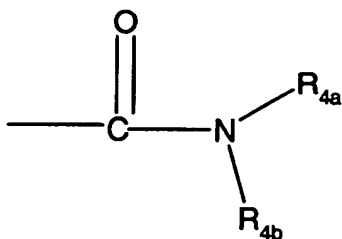


,

where  $\text{R}_{40}$  is hydrogen or  $\text{C}_1$  -  $\text{C}_8$  alkyl.

Preferred as the (acylamino acid group) in the group  $\text{R}_4$

5 is the group:



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wherein  $R^{4a}$  is selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl; and wherein  $NR^{4b}$  is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred  $R^{4a}$  group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and derivatives thereof.

A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

Particularly preferred are  $R^{4b}$  groups that combine with the nitrogen atom to represent amino acid groups selected from: glycine, glycine methyl ester, L-alanine, L-alanine methylester, L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl ester, L-phenyl alanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L-valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.



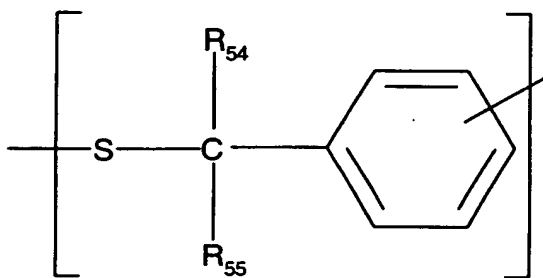
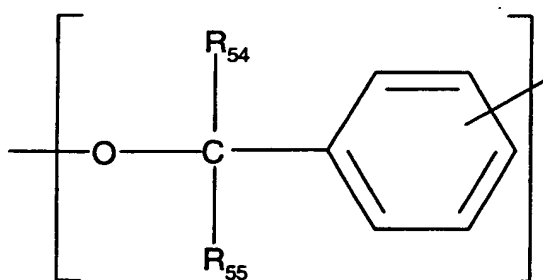
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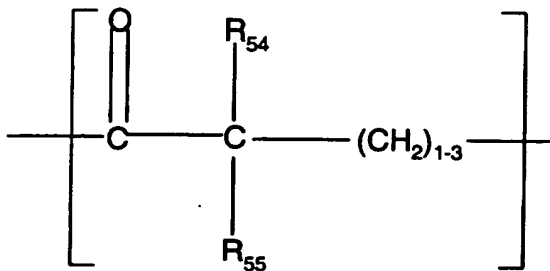
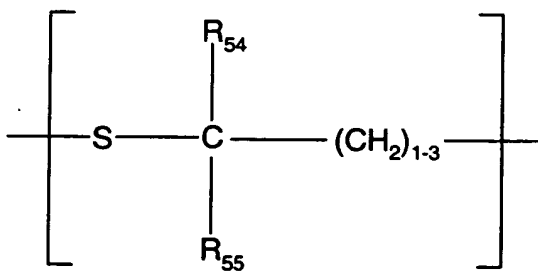
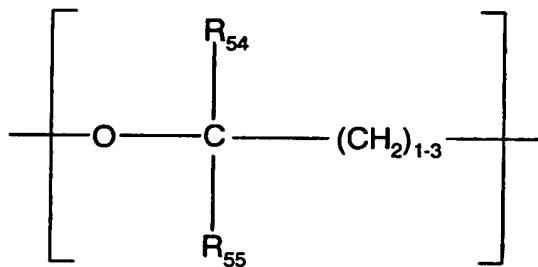
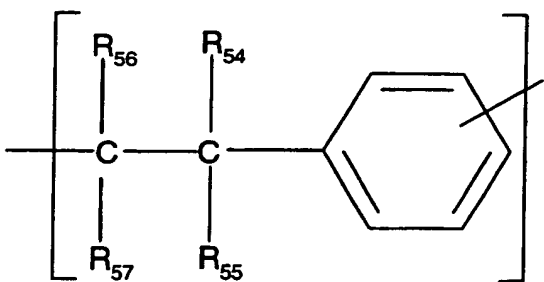
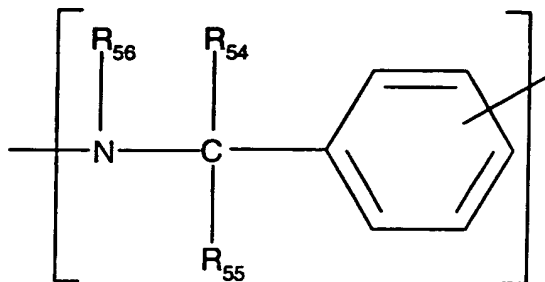
**Preferred R<sub>5</sub> Substituents:**

Preferred acid linker,  $-(L_a)-$ , for R<sub>5</sub> is selected from the group consisting of;

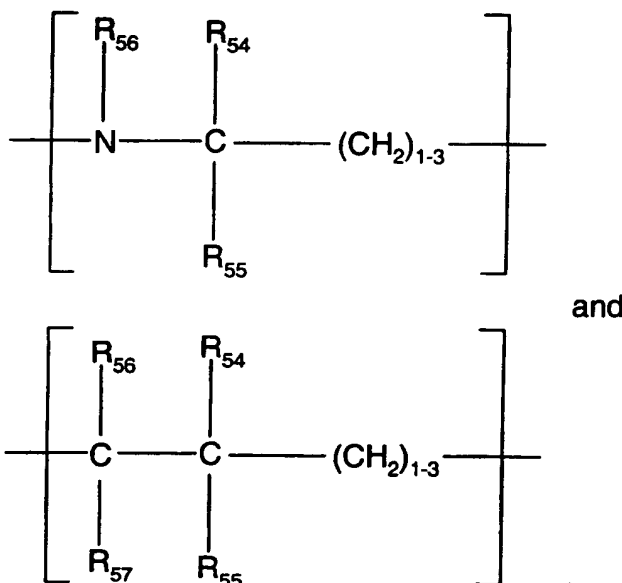
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wherein R<sub>54</sub>, R<sub>55</sub>, R<sub>56</sub> and R<sub>57</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, or halo. Preferred (acidic group) for R<sub>5</sub> is selected from the group consisting of -CO<sub>2</sub>H, -SO<sub>3</sub>H and -P(O)(OH)<sub>2</sub>

**Preferred R<sub>6</sub> and R<sub>7</sub> substituents:**

Another preferred subclass of compounds of formula (III) are those wherein for R<sub>6</sub> and R<sub>7</sub> the non-interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C<sub>4</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>7</sub>-C<sub>12</sub> aralkyl, C<sub>7</sub>-C<sub>12</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkenyloxy, C<sub>2</sub>-C<sub>6</sub> alkynyloxy, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub>

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- alkoxyalkyloxy, C<sub>2</sub>-C<sub>12</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>12</sub>  
alkylcarbonylamino, C<sub>2</sub>-C<sub>12</sub> alkoxyamino, C<sub>2</sub>-C<sub>12</sub>  
alkoxyaminocarbonyl, C<sub>1</sub>-C<sub>12</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> alkylthio,  
C<sub>2</sub>-C<sub>12</sub> alkylthiocarbonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>  
5 alkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub>  
haloalkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl,  
-C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl), benzyloxy,  
phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino,  
bromo, carbamyl, carboxyl, carbalkoxy, -(CH<sub>2</sub>)<sub>n</sub>-CO<sub>2</sub>H,  
10 chloro, cyano, cyanoguanidinyll, fluoro, guanidino,  
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,  
iodo, nitro, phosphono, -SO<sub>3</sub>H, thioacetal, thiocarbonyl,  
and carbonyl; where n is from 1 to 8.

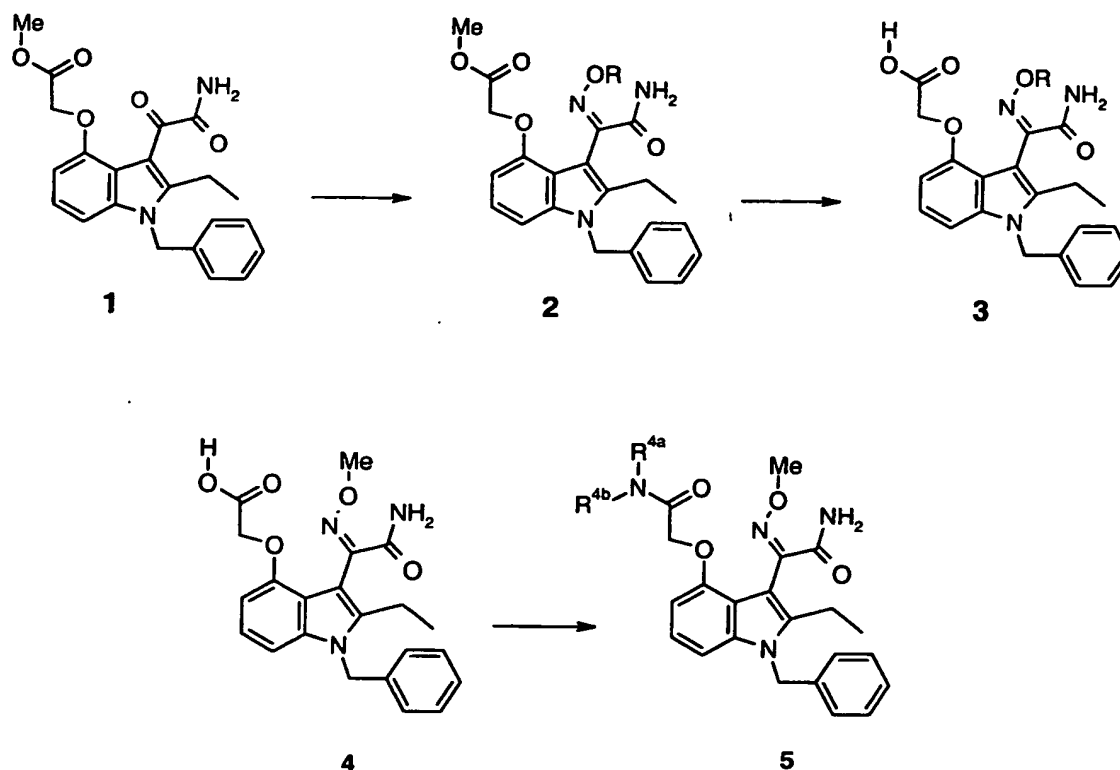
- 15 Most preferred as non-interfering substituents are  
methyl, ethyl, propyl, and isopropyl.

The indole-3-oxime compounds of the invention can be  
prepared following protocol of scheme 2 below;

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Scheme 2



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To introduce the oxime functionality, the methyl ester of the glyoxylamide (compound 10 in scheme 1, compound 1 in scheme 2, *supra.*) is heated with hydroxylamine hydrochloride (when R is H) in a THF/methanol mixture for 8 hours or until the reaction was deemed complete. The reaction product is isolated by chromatography or other known laboratory procedure to afford a white solid. Substituted oximes such as when R is methyl, ethyl, phenyl or other substituent can be prepared by reacting the corresponding substituted hydroxylamine hydrochloride or free base with the

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glyoxylamide as described *supra*. The ester functionality at the 4 or 5 position on the indole nucleus, as in for example, compound 2, can be: (a) converted to the acid by hydrolysis using lithium hydroxide or other known ester hydrolysis methods to afford compounds of formula 3, or (b) converted to an amide functionality directly or via the acid functionality to afford compounds of formula 4. General procedures for the conversion of organic acids to amino acid are well known to artisans in the field, and have been documented in general reference texts including, for example, J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989.

15

The oxime acid compounds of formula 3 such as the methyloxime compound such as that of formula 4 can be converted to the corresponding amino acid derivative via the methylester by coupling with various amino acids by general coupling procedures known to one skilled in the art. Additional references, or procedures are found in J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985; R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989 and J. Jones Amino Acids and Peptide

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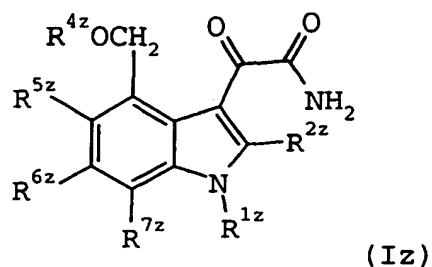
Synthesis, Oxford Science Publications, Stephen G. Davis,  
Editor, Oxford University Press Inc., New York, NY, 1992.

5    **III. Method of Making the 1H-Indole-3-Glyoxylamide  
Starting Material for Preparing the Compounds of the  
Invention:**

          The synthesis of the indole compounds of the  
10    invention (viz., Compounds of Formulae I and II) can be  
accomplished by well known methods as recorded in the  
chemical literature. In particular, the indole starting  
materials may be prepared by the synthesis schemes  
taught in US Patent No. 5,654,326; the disclosure of  
15    which is incorporated herein by reference. Another  
method of making 1H-indole-3-glyoxylamide sPLA<sub>2</sub>  
inhibitors is described in United States Patent  
Application Serial No. 09/105381, filed June 26, 1998  
and titled, "Process for Preparing 4-substituted 1-H-  
20    Indole-3-glyoxylamides" the entire disclosure of which is  
incorporated herein by reference.

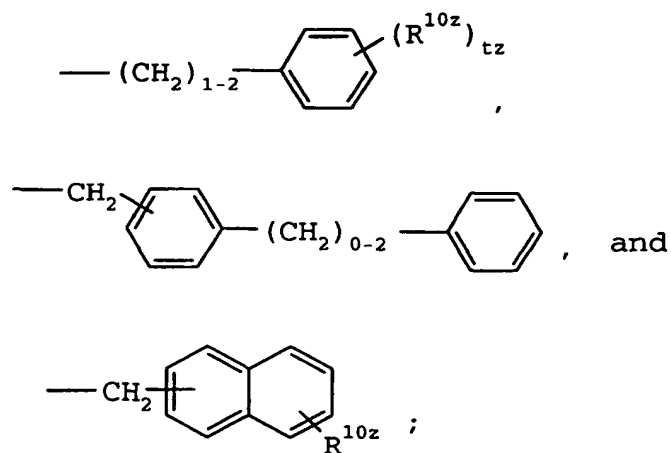
          United States Patent Application Serial  
No. 09/105381 discloses the following process having  
25    steps (a) thru (i):  
Preparing a compound of the formula (Iz) or a  
pharmaceutically acceptable salt or prodrug derivative  
thereof

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5 wherein:

$R^{1z}$  is selected from the group consisting of -C<sub>7</sub>-C<sub>20</sub> alkyl,



where

10  $R^{10z}$  is selected from the group consisting of halo, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>10</sub> alkyl) and halo(C<sub>1</sub>-C<sub>10</sub>)alkyl, and tz is an integer from 0 to 5 both inclusive;

15  $R^{2z}$  is selected from the group consisting of hydrogen, halo, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>4</sub> cycloalkyl, C<sub>3</sub>-C<sub>4</sub>



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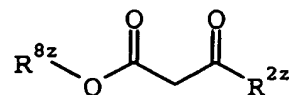
cycloalkenyl, -O-(C<sub>1</sub>-C<sub>2</sub> alkyl), -S-(C<sub>1</sub>-C<sub>2</sub> alkyl), aryl, aryloxy and HET;

R<sup>4z</sup> is the group -CO<sub>2</sub>H, or salt and prodrug derivative thereof; and

5 R<sup>5z</sup>, R<sup>6z</sup> and R<sup>7z</sup> are each independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo(C<sub>2</sub>-C<sub>6</sub>)alkyl, bromo, chloro, fluoro, iodo and aryl;

which process comprises the steps of:

10 a) halogenating a compound of formula Xz

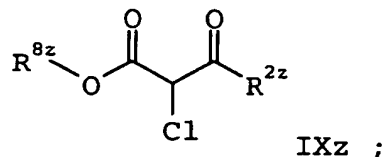


Xz

where R<sup>8z</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl or HET;

with SO<sub>2</sub>Cl<sub>2</sub> to form a compound of formula

15 IX

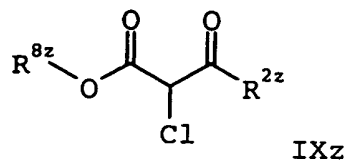


IXz ;

b) hydrolyzing and decarboxylating a compound of formula IXz

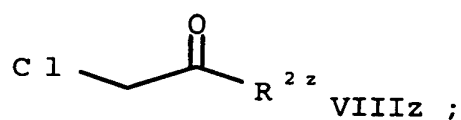
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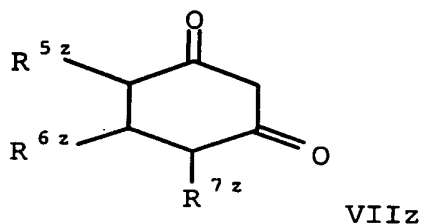


to form a compound of formula VIIIz

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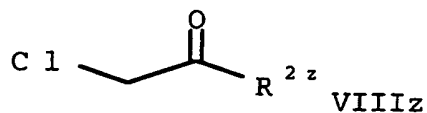


c) alkylating a compound of formula VIIz

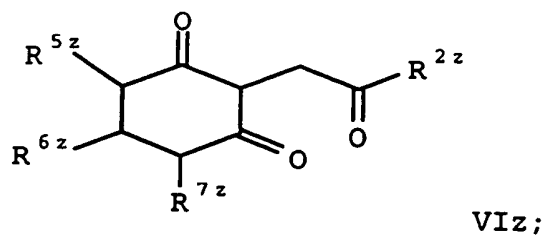


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with a compound of formula VIIIz



to form a compound of formula VIz

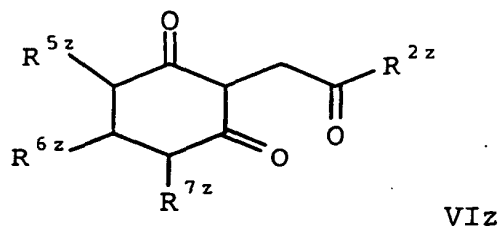


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- d) aminating and dehydrating a compound of formula VIz

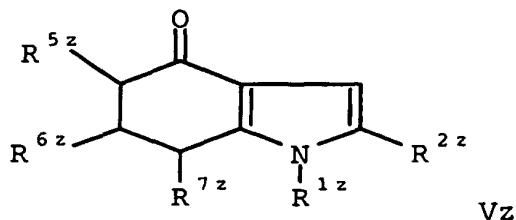


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with an amine of the formula  $R^{1z}NH_2$  in the presence of a solvent that forms an azeotrope with water to form a compound of formula Vz;

10

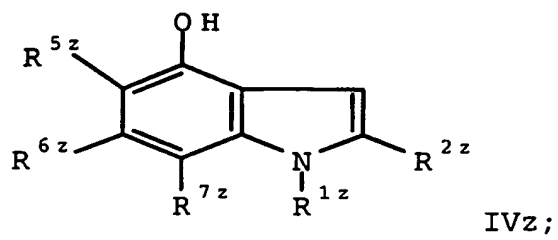
- e) oxidizing a compound of formula Vz



15

by refluxing in a polar hydrocarbon solvent having a boiling point of at least 150 °C and a dielectric constant of at least 10 in the presence of a catalyst to form a compound of formula IVz

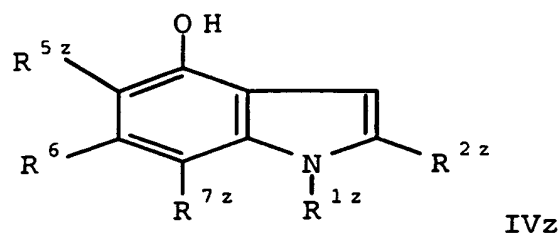
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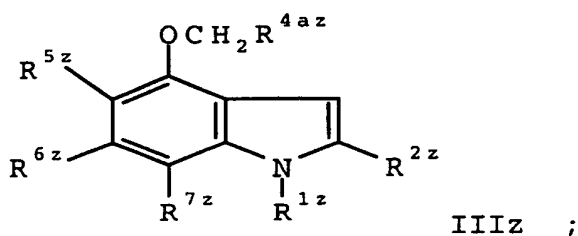
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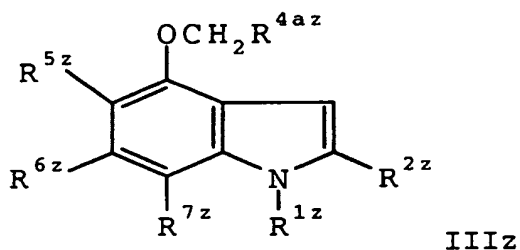
f) alkylating a compound of the formula IVz



with an alkylating agent of the formula  $XCH_2R^{4az}$   
 where X is a leaving group and  $R^{4az}$  is  $-CO_2R^{4bz}$ ,  
 where  $R^{4bz}$  is an acid protecting group to form a  
 compound of formula IIIz

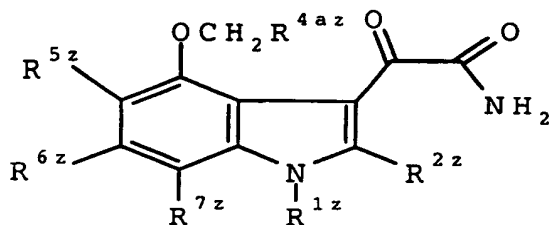


g) reacting a compound of formula IIIz



with oxalyl chloride and ammonia to form a  
 compound of formula IIz

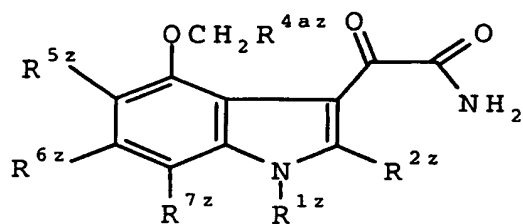
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IIz; and

5

- h) optionally hydrolyzing a compound of formula IIz



10

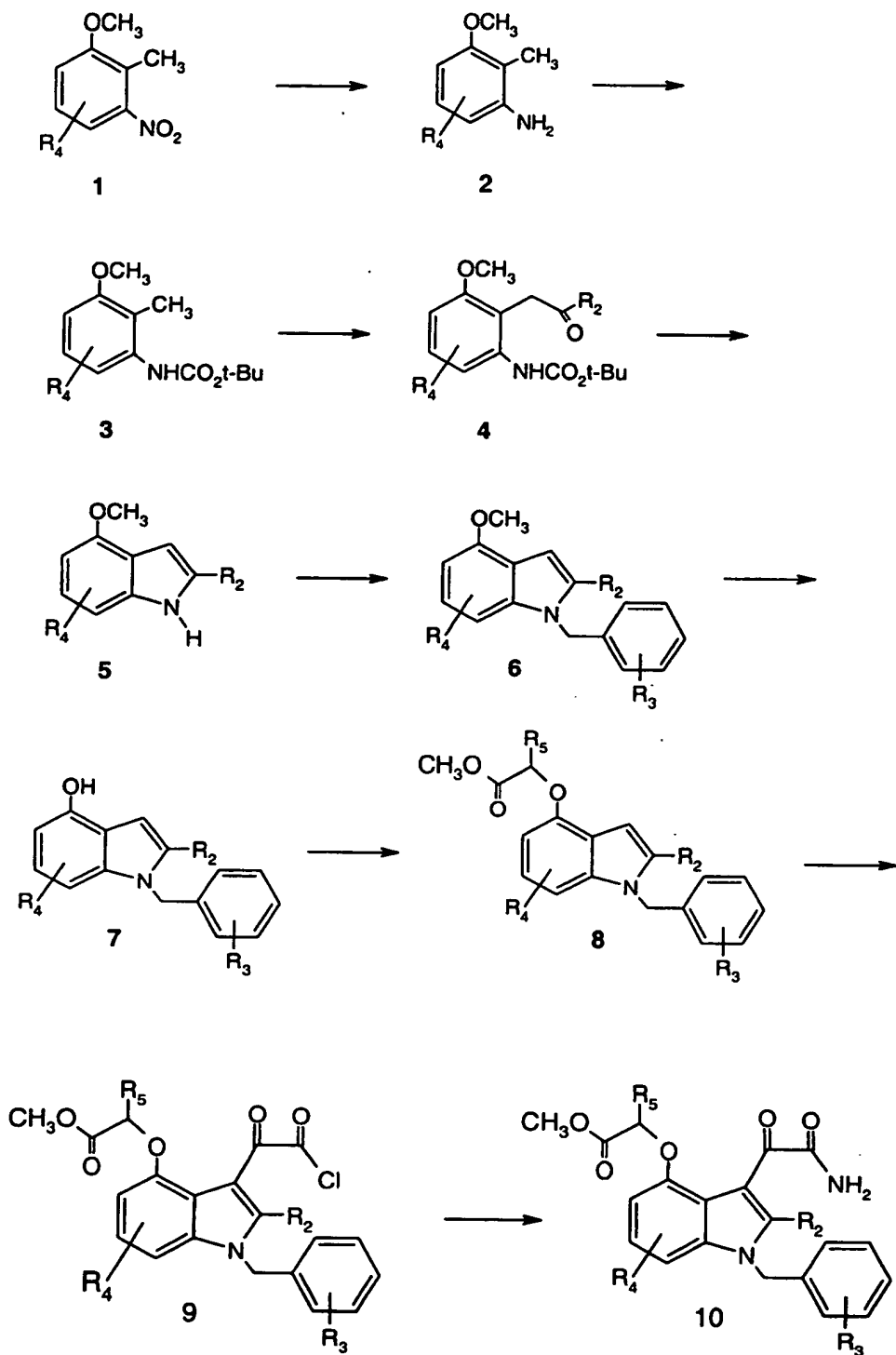
IIz

to form a compound of formula Iz.

An alternative protocol useful for the synthesis of the starting material is shown in Scheme 1 below:

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## Scheme 1



5 The synthesis of indole-3-oxime amides (compound of formula I and II, supra.) of this invention uses

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as starting material the glyoxamide ((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)acetic acid methyl ester, compound 10, *supra*. This starting material is prepared as set out in the preceding section or by the method of Example 9 of U.S. Patent No. 5,654,326 (the disclosure of which is incorporated herein by reference).

To obtain the glyoxylamide starting material substituted in the 4-position with an (acidic group) linked through an oxygen atom, the reactions outlined in the scheme *supra*, are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, *Synthesis*, 1991, 871-878, the disclosures of which are incorporated herein by reference). The starting material ortho-nitrotoluene, 1, is readily reduced to 2-methyl,3-methoxyaniline, 2. Reduction of 1 is by the catalytic hydrogenation of the corresponding nitrotoluene using palladium on carbon as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline 2, obtained, is converted to the N-tert-butyloxycarbonyl derivative 3, in good yield, on heating with di-tert-butyl dicarbonate in THF at reflux temperature. The dilithium salt of the dianion of 3 is



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generated at -40 to -20°C in THF using sec-butyllithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide to form the ketone 4. This product (4) may be purified by crystallization from hexane, or reacted  
5 directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25°C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated with  
10 an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100°C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-demethylated by stirring with boron tribromide in methylene chloride for  
15 approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, *Adv. Drug Res.*, 1977, 12, 176, the disclosure of which is incorporated herein by reference). The 4-hydroxyindole, 7, is alkylated with an alpha bromoalkanoic acid ester in dimethylformamide (DMF) using  
20 sodiumhydride as a base, with reaction condition of 5 to 6. The  $\alpha$ -[(indol-4-yl)oxy]alkanoic acid ester, 8, is reacted with oxalyl chloride in methylene chloride to give 9, which is not purified but reacted directly with ammonia to give the glyoxamide 10.

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Glyoxamide starting material compounds substituted at the 5 position of the indole nucleus with an (acidic group) may be prepared by methods and starting materials shown in schemes 2 and 3 of Patent No. 5,654,326; the disclosure of which is incorporated herein by reference.

#### **IV. Methods of Using the Compounds of the Invention:**

The indole compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) sPLA<sub>2</sub>, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting sPLA<sub>2</sub> mediated release of fatty acids comprises contacting mammalian sPLA<sub>2</sub> with an therapeutically effective amount of indole compounds corresponding to Formulae (I) or (II) as described herein including salt or a prodrug derivative thereof.

Another aspect of this invention is a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress

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syndrome, pancreatitis, trauma, bronchial asthma,  
allergic rhinitis, rheumatoid arthritis, osteoarthritis,  
and related diseases which comprises administering to a  
mammal (including a human) a therapeutically effective  
5 dose of the indole compound of the invention (see,  
formulae I and II).

As previously noted the compounds of this invention  
are useful for inhibiting sPLA<sub>2</sub> mediated release of  
10 fatty acids such as arachidonic acid. By the term,  
"inhibiting" is meant the prevention or therapeutically  
significant reduction in release of sPLA<sub>2</sub> initiated  
fatty acids by the compounds of the invention. By  
"pharmaceutically acceptable" it is meant the carrier,  
15 diluent or excipient must be compatible with the other  
ingredients of the formulation and not deleterious to  
the recipient thereof.

The specific dose of a compound administered  
20 according to this invention to obtain therapeutic or  
prophylactic effects will, of course, be determined by the  
particular circumstances surrounding the case, including,  
for example, the compound administered, the route of  
administration and the condition being treated. Typical  
25 daily doses will contain a non-toxic dosage level of from

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about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention (per Formula I or II) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the indole compound of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical

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formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound.

The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also

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act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

5           Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or  
10   acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

          In powders the carrier is a finely divided solid which is in admixture with the finely divided Active  
15   ingredient. In tablets the Active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active  
20   ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa  
25   butter.

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Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended  
5 in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely  
10 divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 thru 8 are illustrative only and are not intended to limit the  
15 scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or (II) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

**Formulation 1**

20 Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	<u>250</u>
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

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**Formulation 2**

A tablet is prepared using the ingredients below:

	<u>Quantity (mg/tablet)</u>
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

5

The components are blended and compressed to form tablets each weighing 665 mg

**Formulation 3**

10        An aerosol solution is prepared containing the following components:

	<u>Weight</u>
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

15        The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and



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diluted with the remainder of the propellant. The valve units are then fitted to the container.

**Formulation 4**

- 5           Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

- The Active ingredient, starch and cellulose are
- 10   passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and
- 15   passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each
- 20   weighing 150 mg.

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**Formulation 5**

Capsules, each containing 80 mg of Active ingredient,  
are made as follows:

5

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

The Active ingredient, cellulose, starch, and  
magnesium stearate are blended, passed through a No. 45  
mesh U.S. sieve, and filled into hard gelatin capsules in  
10 200 mg quantities.

**Formulation 6**

Suppositories, each containing 225 mg of Active  
ingredient, are made as follows:

15

Active ingredient	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

The Active ingredient is passed through a No. 60 mesh  
U.S. sieve and suspended in the saturated fatty acid  
glycerides previously melted using the minimum heat  
necessary. The mixture is then poured into a suppository  
20 mold of nominal 2 g capacity and allowed to cool.

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**Formulation 7**

Suspensions, each containing 50 mg of Active ingredient per 5 ml dose, are made as follows:

5

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

10

**Formulation 8**

An intravenous formulation may be prepared as follows:

15

Active ingredient	100 mg
Isotonic saline	1,000 ml

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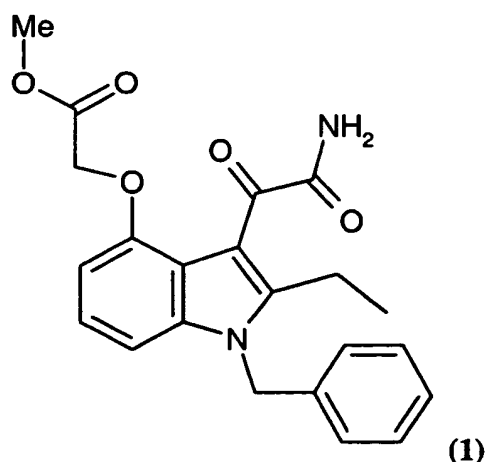
The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

5 All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory nmr and IR spectra. They also had the correct mass spectral values.

10

**Example 1**

Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, a compound represented by the compound of formula (1) formula:



15

**Part A. Preparation of 2-Ethyl-4-methoxy-1H-indole.**

A solution of 140 mL (0.18 mol) of 1.3M sec-butyl lithium in cyclohexane was added slowly to N-tert-butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol)

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in 250 mL of THF keeping the temperature below  $-40^{\circ}\text{C}$  with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to  $0^{\circ}\text{C}$  and then the bath replaced. After the temperature had cooled to  $-60^{\circ}\text{C}$ ,  
5 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of ether and 400 mL of 0.5N HCl.  
10 The organic layer was separated, washed with water, brine, dried over  $\text{MgSO}_4$ , and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(tert-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of  
15 trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was chromatographed three  
20 times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for  $\text{C}_{11}\text{H}_{13}\text{NO}$ :

Calculated: C, 75.40; H, 7.48; N, 7.99

Found: C, 74.41; H, 7.64; N, 7.97.

25

**Part B. Preparation of 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.**

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2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/mineral oil was added. After 1.5 hours, 2.9 mL (24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried (MgSO<sub>4</sub>) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

**Part C. Preparation of 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole.**

3.1g (11.7 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole was O-demethylated by treating it with 48.6 mL of 1M BBr<sub>3</sub> in methylene chloride with stirring at room temperature for 5 hours, followed by concentration at reduced pressure. The residue was dissolved in ethyl acetate, washed with brine and dried (MgSO<sub>4</sub>). After concentrating at reduced pressure, the residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to give 1.58g (54% yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole, mp, 86-90°C.

Analyses for C<sub>17</sub>H<sub>17</sub>NO:

Calculated: C, 81.24; H, 6.82; N, 5.57  
Found: C, 81.08; H, 6.92; N, 5.41.

**Part D. Preparation of [[2-Ethyl-1-(phenylmethyl)-**

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**1H-indol-4-yl]oxy]acetic acid methyl ester.**

2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole (1.56g, 6.2 mmol) was added to a mixture of 248mg (6.2 mmol) of 60% NaH/mineral oil in 20mL DMF and stirred for 0.67 hour.

5

Then 0.6 mL(6.2 mmol) of methyl bromoacetate was added and stirring was continued for 17 hours. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried (MgSO<sub>4</sub>), and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc/hexane, to give 1.37g (69% yield) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, 89-92°C.

15 Analyses for C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub>:

Calculated: C, 74.28; H, 6.55; N, 4.33

Found: C, 74.03; H, 6.49; N, 4.60.

**Part E. Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.**

Oxalyl chloride (0.4 mL, 4.2 mmol) was added to 1.36g (4.2 mmol) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester in 10 mL of methylene chloride and the mixture stirred for 1.5 hours. The mixture was concentrated at reduced pressure and residue taken up in 10 mL of methylene chloride. Anhydrous ammonia was bubbled in for 0.25 hours, the mixture stirred

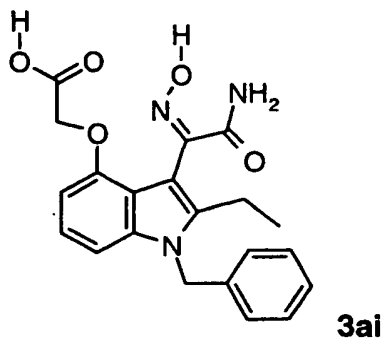
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for 1.5 hours and evaporated at reduced pressure. The residue was stirred with 20 mL of ethyl acetate and the mixture filtered. The filtrate was concentrated to give 1.37g of a mixture of [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and ammonium chloride. This mixture melted at 172-187°C.

**Example 2**

10 (indol-3-oxime amide starting material)

2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

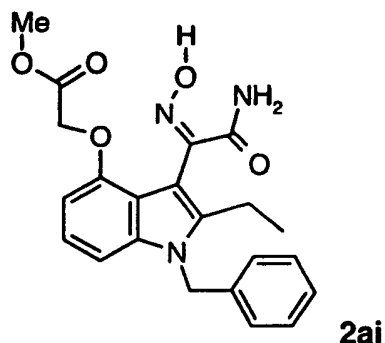


A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.



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A stirred mixture of **1** (600 mg, 1.52 mmol) and hydroxylamine hydrochloride (528 mg, 7.60 mmol) in THF (4 mL)/CH<sub>3</sub>OH (4 mL) was heated at 55 °C for 8 h. After concentration at ambient temperature, the residue was chromatographed on silica (gradient 0-40% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound **2ai** (285 mg) as a white solid in 46% yield. IR (CHCl<sub>3</sub>) 3510, 3415, 1757, 1667 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.17 (t, *J* = 7.5 Hz, 3H), 2.84 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.73 (s, 2H), 5.36 (s, 2H), 5.67 (br s, 1H), 6.31 (br s, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.98-7.07 (m, 3H), 7.23-7.32 (m, 3H); ESIMS *m/e* 410 (M<sup>+</sup>+1).

Elemental Analyses for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>·0.30(H<sub>2</sub>O):

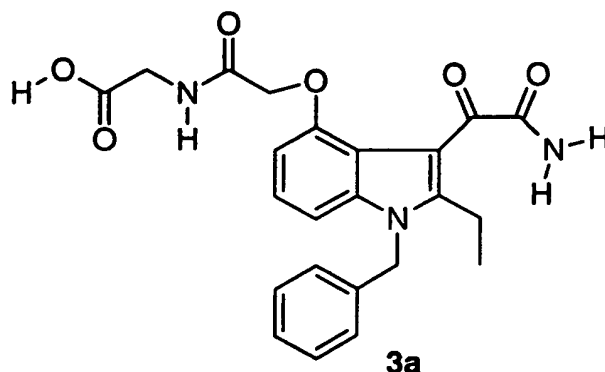
Calculated: C, 63.70; H, 5.73; N, 10.13;  
Found: C, 63.68; H, 5.62; N, 10.20.

### Example 3

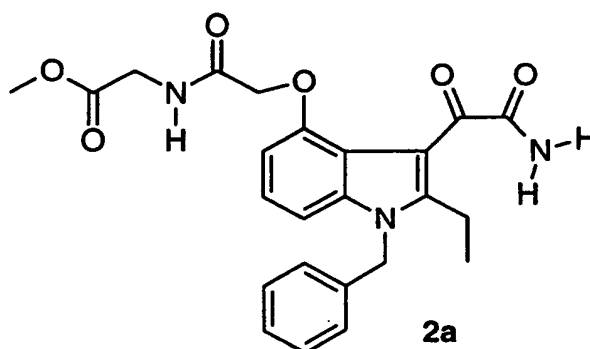
*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine

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**A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester**



5

To a solution of **1** (0.100 g, 0.249 mmol) in 2 mL DMF was added collidine (0.069 mL, 0.523 mmol), methyl glycine hydrochloride (0.0313 g, 0.249 mmol), and benzotriazolyl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.115 g, 0.261) sequentially at room temperature. After 2.5 hrs. the reaction mixture was concentrated in vacuo to near dryness, then it was taken up in CH<sub>2</sub>Cl<sub>2</sub>, chromatographed on a silica gel column (gradient 20-40% THF in CH<sub>2</sub>Cl<sub>2</sub>) and dried in an 80°C vacuum oven to give 0.0768 g of **2a** as a yellow solid in 68% yield. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.04 (t, *J* = 6.8 Hz, 3H), 2.90 (br q, *J* = 6.8 Hz, 2H),

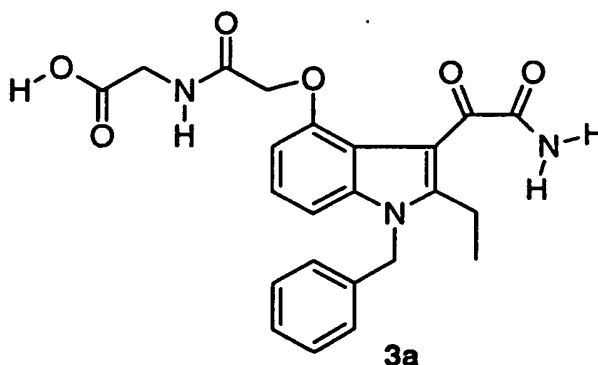
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3.57 (s, 3H), 3.88 (d,  $J = 5.5$  Hz, 2H), 4.57 (s, 2H), 5.51 (s, 2H), 6.59 (d,  $J = 5.6$  Hz, 1H), 7.01-7.08 (m 4H), 7.19-7.30 (m, 3H), 7.55 (s, 1H), 7.99 (s, 1H), 8.40 (t,  $J = 5.5$  Hz, 1H).

5

**B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine**



10 To a solution of 2a (0.035 g, 0.078 mmol) in 1 mL THF, 1 mL MeOH and 0.25 mL distilled H<sub>2</sub>O was added 4.17N LiOH (0.093 mL, 0.388 mmol) at room temperature. After 2 hrs. the reaction mixture was acidified with 5N HCl (0.093 mL, 0.465 mmol) and concentrated *in vacuo*. The residue  
15 was taken up in CH<sub>2</sub>Cl<sub>2</sub>, then rapidly triturated with hexanes to give a yellow suspension which was filtered and dried in an 80°C vacuum oven to give 0.0336 g of 3a as a yellow solid in 99% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.04 (t,  $J = 5.9$  Hz, 3H), 2.90 (br q,  $J = 5.9$  Hz, 2H), 3.80 (d,  $J = 4.8$  Hz, 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d,  $J = 5.8$  Hz, 1H),  
20

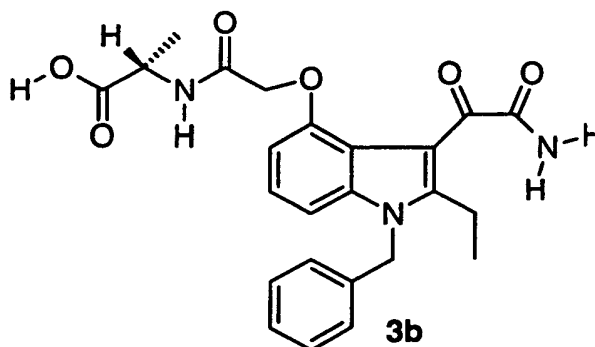
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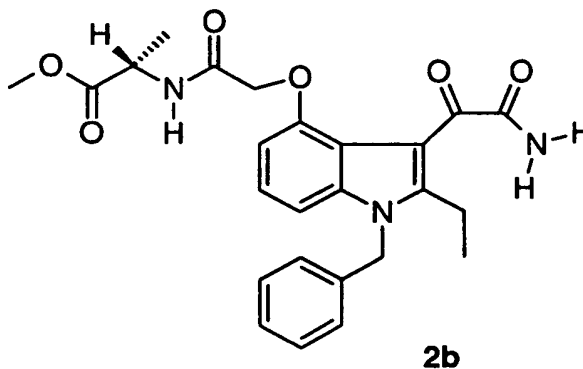
7.01-7.28 (m, 7H), 7.54 (s, 1H), 7.99 (s, 1H), 8.31 (t,  $J$  = 4.8 Hz, 1H), 12.25-12.75 (br s, 1H).

**Example 4**

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine



A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester



Following the experimental procedure as described for 2a, 2b was obtained as a yellow solid in 65% yield.

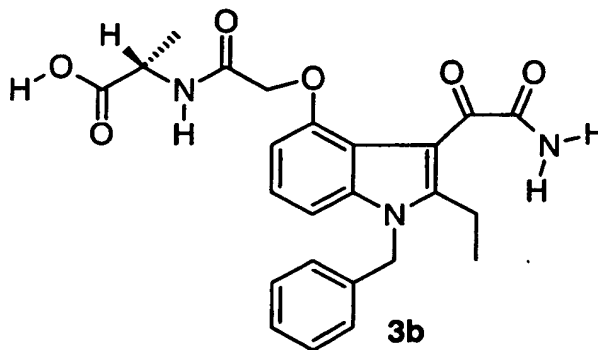
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  1.04 (t,  $J$  = 7.2 Hz, 3H), 1.29 (d,  $J$  = 7.3 Hz, 3H), 2.91 (br q,  $J$  = 7.2 Hz, 2H), 3.54 (s, 3H), 4.29 (qd,  $J$  = 7.3, 6.8 Hz, 1H), 4.55 (s, 2H), 5.51 (s,

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2H), 6.57 (m, 1H), 6.99 (d,  $J = 7.4$  Hz, 2H), 7.07-7.08 (m, 2H), 7.21-7.31 (m, 3H), 7.56 (s, 1H), 8.05 (s, 1H), 8.40 (d,  $J = 6.8$  Hz, 1H).

5        **B.    Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine**

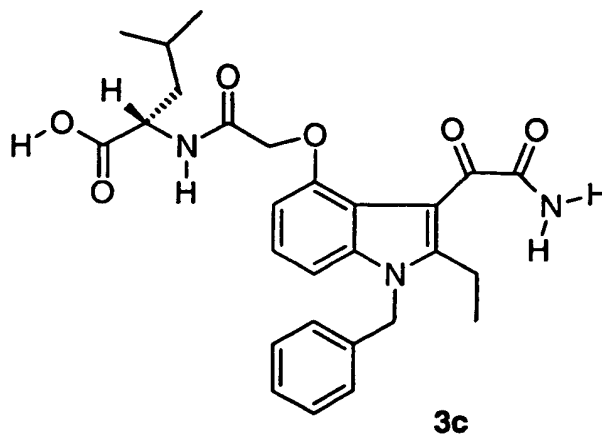


Following the experimental procedure as described for  
10    preparing compound 3a, compound 3b, was obtained as a  
yellow solid in 89% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.04 (t,  $J$   
= 7.2 Hz, 3H), 1.29 (d,  $J = 7.3$  Hz, 3H), 2.91 (br q,  $J$   
= 7.2 Hz, 2H), 4.22 (td,  $J = 7.2, 7.1$  Hz, 1H), 4.54 (s, 2H),  
5.51 (s, 2H), 6.60 (d,  $J = 6.3$  Hz, 1H), 7.00-7.09 (m, 4H),  
15    7.21-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.31 (d,  $J$   
= 7.1 Hz, 1H), 12.75-12.84 (br s, 1H).

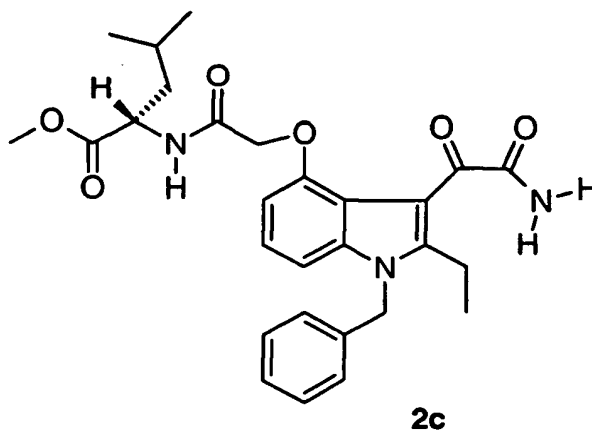
**Example 5**

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
20    indol-4-yl]oxy]acetyl]-L-leucine

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A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester

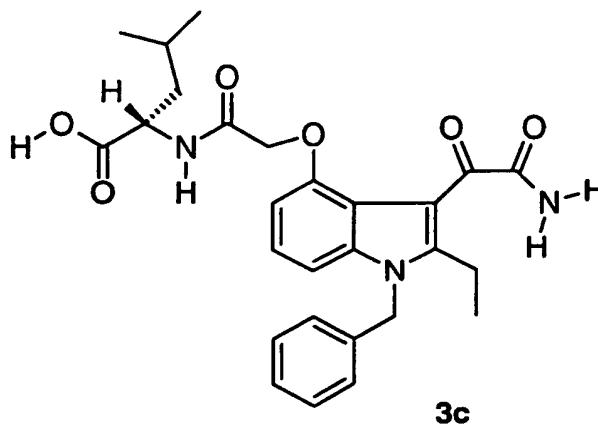


5

Following the experimental procedure as described for 2a, 2c was obtained as a yellow solid in 98% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.67 (d, *J* = 5.5 Hz, 3H), 0.72 (d, *J* = 5.7 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.30-1.50 (m, 2H), 1.51-1.64 (m, 1H), 2.91 (br q, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 4.20-4.27 (m, 1H), 4.57 (s, 2H), 5.52 (s, 2H), 6.53-6.56 (m, 1H), 6.97-7.08 (m, 4H), 7.21-7.29 (m, 3H), 7.56 (s, 1H), 8.07 (s, 1H), 8.37 (d, *J* = 7.3 Hz, 1H).

10

**B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-leucine**



5 Following the experimental procedure as described for 3a, 3c was obtained as a yellow solid in 75% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.76 (d, *J* = 5.7 Hz, 3H), 0.78 (d, *J* = 6.1 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.39-1.43 (m, 1H), 1.69 (t, *J* = 7.3 Hz, 2H), 2.96 (br q, *J* = 7.3 Hz, 2H), 4.57-4.65 (m, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 5.38 (s, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.95-7.12 (m, 5H), 7.26-7.32 (m, 3H), 8.17 (d, *J* = 8.2 Hz, 1H).

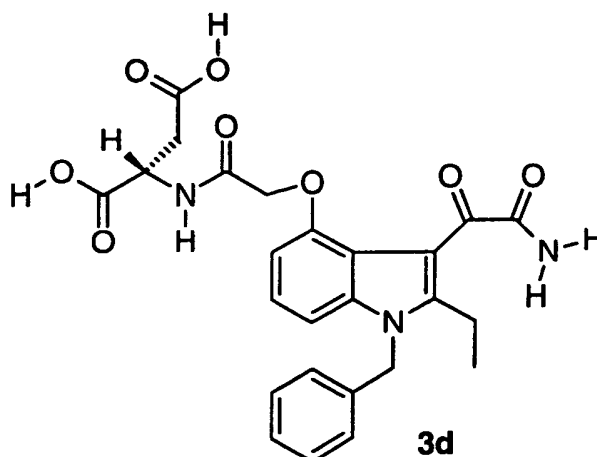
15

**Example 6**

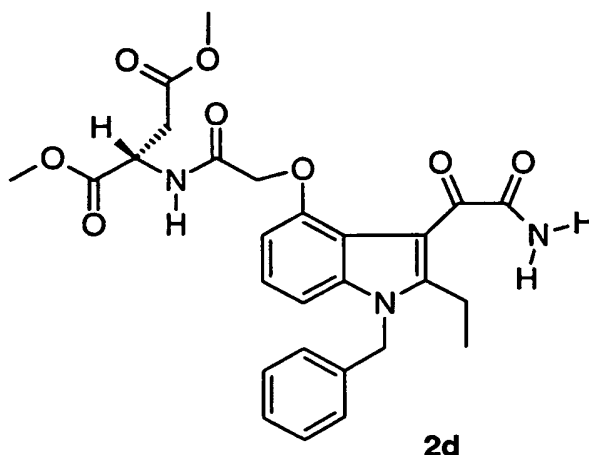
*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-aspartic acid

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**A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-aspartic acid dimethyl ester**



5

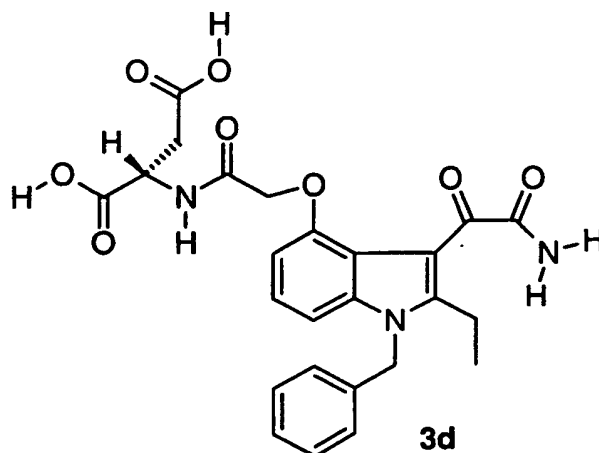
Following the experimental procedure as described for 2a, 2d was obtained as a yellow solid in 88% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t, *J* = 7.3 Hz, 3H), 2.72 (dd, *J* = 16.6, 7.1 Hz, 1H), 2.83 (dd, *J* = 16.7, 7.1 Hz, 1H), 2.90 (br q, *J* = 7.3 Hz, 2H), 3.49 (s, 3H), 3.55 (s, 3H), 4.54 (s, 2H), 4.66 (m, 1H), 5.51 (s, 2H), 6.54 (m, 1H), 6.97-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.50 (s, 1H), 7.97 (s, 1H), 8.52 (d, *J* = 7.9 Hz, 1H).



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**B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-aspartic acid**



5

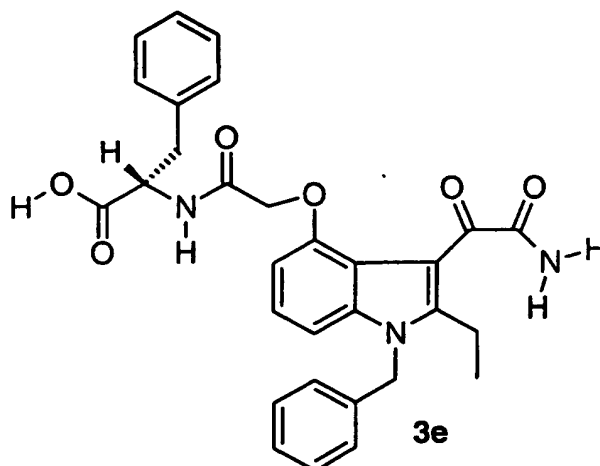
Following the experimental procedure as described for 3a, 3d was obtained as a yellow solid in 99% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t, *J* = 7.2 Hz, 3H), 2.52-2.76 (m, 2H), 2.90 (br q, *J* = 7.2 Hz, 2H), 4.53 (s, 2H), 4.53-4.60 (m, 1H), 5.50 (s, 2H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.19-7.30 (m, 3H), 7.47 (s, 1H), 7.94 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 12.40-13.20 (br s, 2H).

**Example 7**

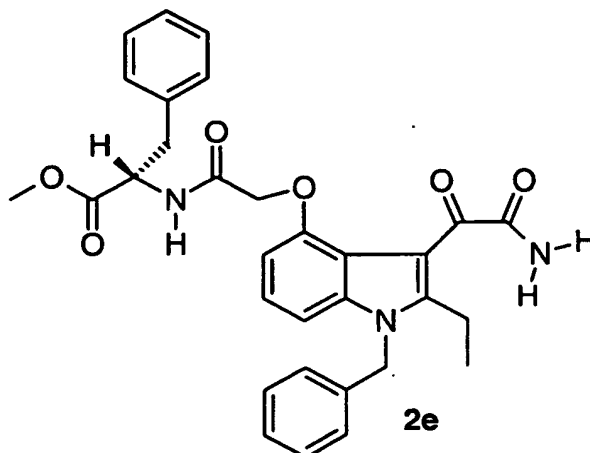
***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-phenylalanine**

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**A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester**



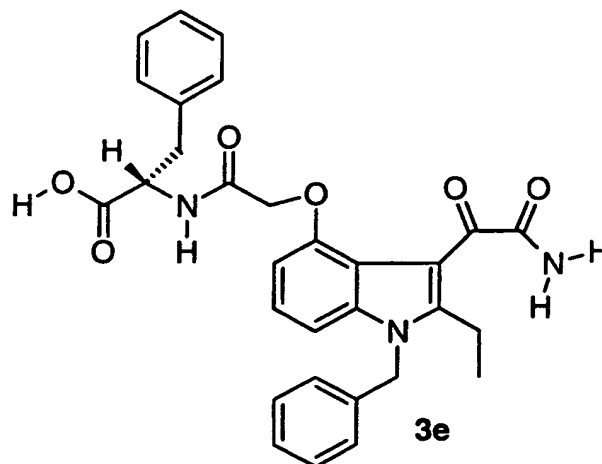
5

Following the experimental procedure as described for 2a, 2e was obtained as a yellow solid in 68% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.06 (t, J = 7.2 Hz, 3H), 2.88-3.03 (m, 4H), 3.54 (s, 3H), 4.47-4.50 (m, 1H), 4.50 (s, 2H), 5.52 (s, 2H), 6.41 (d, J = 7.7 Hz, 1H), 6.98-7.11 (m, 9H), 7.21-7.30 (m, 3H), 7.47 (s, 1H), 8.06 (s, 1H), 8.52 (d, J = 7.7 Hz, 1H).

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**B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-phenylalanine**



5

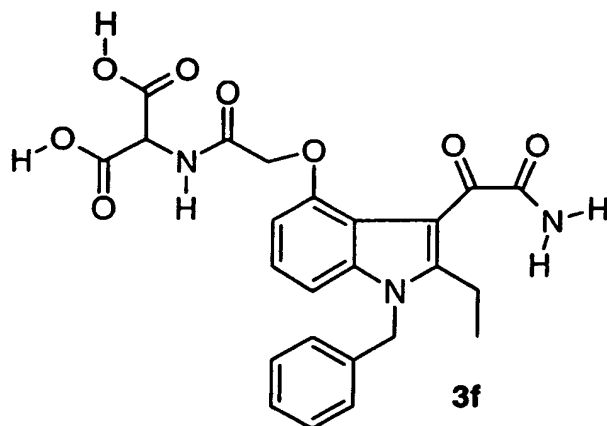
Following the experimental procedure as described for 3a, 3e was obtained as a yellow solid in 93% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t, *J* = 7.1 Hz, 3H), 2.85-3.12 (m, 4H), 4.17-4.26 (m, 1H), 4.54 (s, 2H), 5.51 (s, 2H), 6.59 (d, *J* = 6.4 Hz, 1H), 6.98-7.09 (m, 9H), 7.19-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.30 (d, *J* = 7.0 Hz, 1H), 12.50 (br s, 1H).

**Example 8**

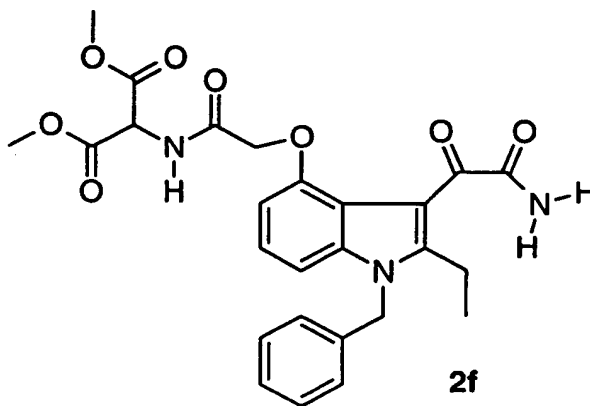
**[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetamido]malonic acid**

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**A. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester**



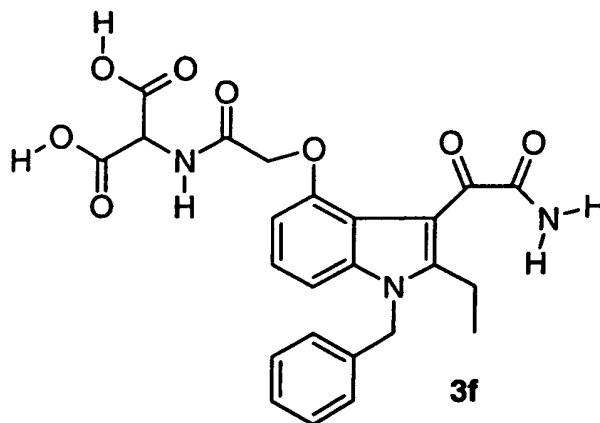
5

Following the experimental procedure as described for 2a, 2f was obtained as a yellow solid in 98% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t, J = 7.3 Hz, 3H), 2.90 (br q, J = 7.3 Hz, 2H), 3.64 (s, 6H), 4.63 (s, 2H), 5.16 (d, J = 7.1 Hz, 1H), 5.51 (s, 2H), 6.54-6.56 (m, 1H), 6.98-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.43 (s, 1H), 7.88 (s, 1H), 8.90 (d, J = 7.2 Hz, 1H).

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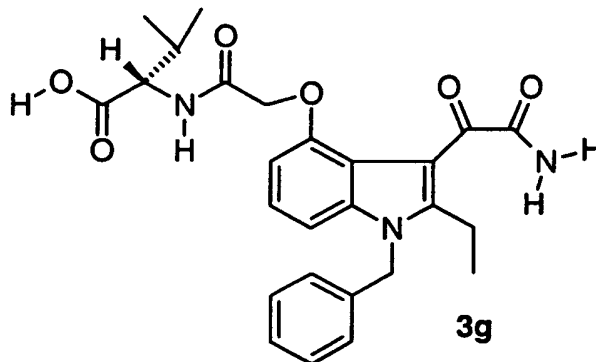
**B. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid**



Following the experimental procedure as described for 3a,  
5 3f was obtained as a yellow solid in 99% yield. <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 1.04 (t, J = 6.9 Hz, 3H), 2.89 (br q, J = 7.3  
Hz, 2H), 4.62 (s, 2H), 4.91 (d, J = 7.2 Hz, 1H), 5.50 (s,  
2H), 6.57 (d, J = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.18-  
7.30 (m, 3H), 7.37 (s, 1H), 7.83 (s, 1H), 8.55 (d, J = 7.2  
10 Hz, 1H), 12.30-13.00 (br s, 2H).

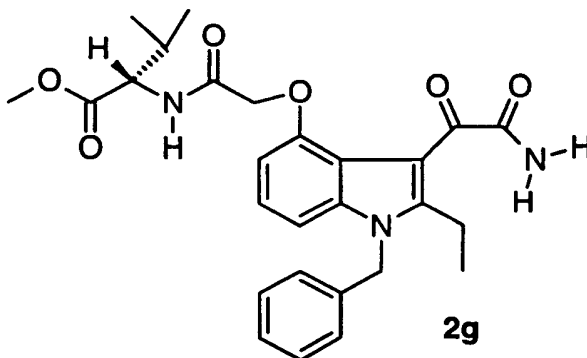
**Example 9**

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine**



5

**A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester**



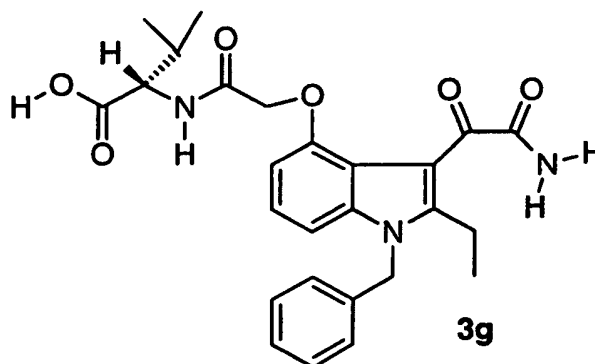
10 Following the experimental procedure as described for 2a,  
2g was obtained as a yellow solid in 96% yield. <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 0.71 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 7.0 Hz,  
3H), 1.05 (t, *J* = 7.2 Hz 3H), 1.99-2.05 (m, 1H), 2.90 (br  
q, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 4.11 (br t, *J* = 7.0 Hz,  
15 1H), 4.60 (s, 2H), 5.52 (s, 2H), 6.52 (d, *J* = 4.4 Hz, 1H),

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6.95 (d,  $J = 7.2$  Hz, 2H), 7.06 (br s, 2H), 7.18-7.29 (m, 3H), 7.52 (s, 1H), 8.04 (s, 1H), 8.20 (d,  $J = 7.8$  Hz, 1H).

**B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine**



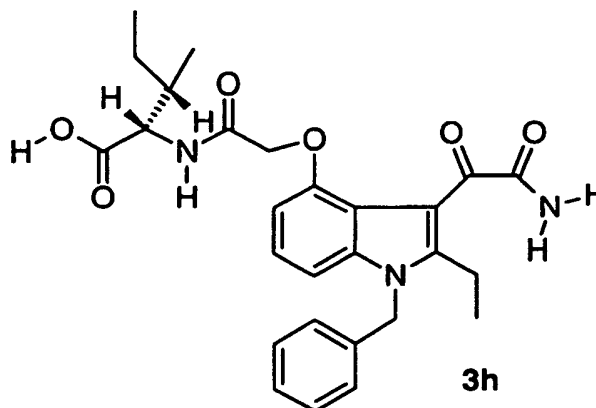
Following the experimental procedure as described for 3a, 3g was obtained as a yellow solid in 94% yield.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  0.71 (d,  $J = 6.9$  Hz, 3H), 0.75 (d,  $J = 6.8$  Hz, 3H), 1.04 (t,  $J = 7.3$  Hz, 3H), 2.01-2.07 (m, 1H), 2.90 (br q,  $J = 7.3$  Hz, 2H), 4.09 (br dd,  $J = 7.9, 6.2$  Hz, 1H), 4.60 (s, 2H), 5.51 (s, 2H), 6.54 (d,  $J = 6.1$  Hz, 1H), 6.95 (d,  $J = 7.3$  Hz, 2H), 6.99-7.08 (m, 2H), 7.18-7.29 (m, 3H), 7.49 (s, 1H), 8.01 (s, 1H), 8.08 (d,  $J = 8.2$  Hz, 1H), 12.63 (br s, 1H).

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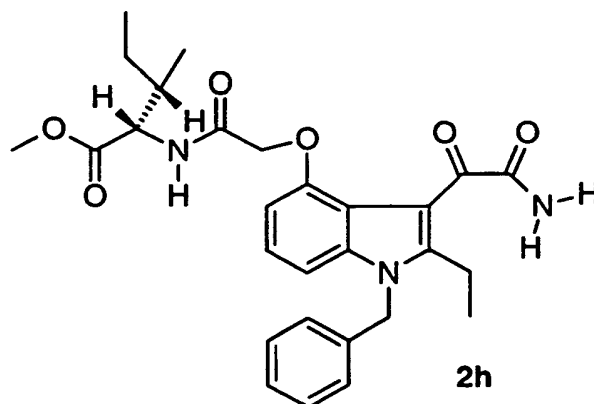
**Example 10**

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-isoleucine**



5

**A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-isoleucine methyl ester**



- 10 Following the experimental procedure as described for 2a, 2h was obtained as a yellow solid in 73% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.64-0.71 (m, 6H), 0.99-1.08 (m, 4H), 1.21-1.26 (m, 1H), 1.76-1.80 (m, 1H), 2.91 (br q, *J* = 7.4 Hz, 2H), 3.53 (s, 3H), 4.15 (br t, *J* = 7.2 Hz, 1H), 4.60 (s,

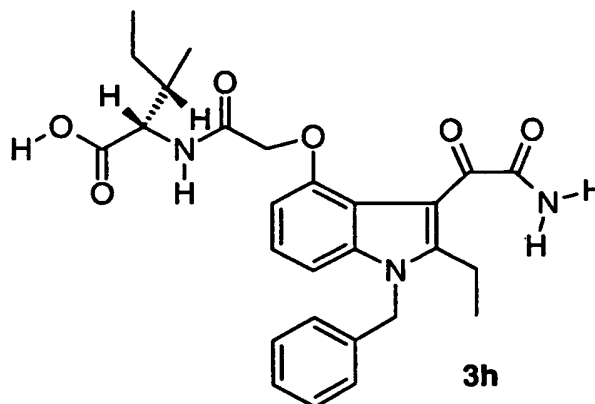


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2H), 5.52 (s, 2H), 6.52 (m, 1H), 6.96 (d,  $J = 7.2$  Hz, 2H), 7.02-7.07 (m, 2H), 7.18-7.29 (m, 3H), 7.53 (s, 1H), 8.04 (s, 1H), 8.23 (d,  $J = 7.7$  Hz, 1H).

5            **B.    Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine**



Following the experimental procedure as described for 3a,  
10    3h was obtained as a yellow solid in 92% yield.  $^1\text{H}$  NMR  
(DMSO- $d_6$ )  $\delta$  0.64-0.84 (m, 6H), 1.04 (t,  $J = 7.2$  Hz, 3H),  
1.21-1.28 (m, 2H), 1.76-1.80 (m, 1H), 2.91 (br q,  $J = 7.2$   
Hz, 2H), 4.12 (br t,  $J = 7.3$  Hz, 1H), 4.59 (s, 2H), 5.51  
(s, 2H), 6.55 (d,  $J = 6.4$  Hz, 1H), 6.96 (d,  $J = 7.2$  Hz,  
15    2H), 7.01-7.08 (m, 2H), 7.21-7.29 (m, 3H), 7.51 (s, 1H),  
8.01 (s, 1H), 8.11 (d,  $J = 7.4$  Hz, 1H), 12.40-12.65 (br s,  
1H).

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**Assay**

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A<sub>2</sub>. The assay described herein

5 has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A<sub>2</sub> on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a

10 Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

## 15 Reagents:

## REACTION BUFFER -

CaCl<sub>2</sub>·2H<sub>2</sub>O (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)

20 (Sigma A-7030, product of Sigma Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

## ENZYME BUFFER -

25 0.05 NaOAc.3H<sub>2</sub>O, pH 4.5

0.2 NaCl

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Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

5 racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-sn-glycero-3-phosphorylcholine

TRITON X-100<sup>TM</sup> prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

10 A measured volume of racemic dipheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar

TRITON X-100<sup>TM</sup> nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB  
15 to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mM Triton X-100<sup>TM</sup> detergent, and 0.12 mM DTMB in a buffered aqueous solution at pH 7.5.

20

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
- 25 3. Add 50 nanograms of sPLA<sub>2</sub> (10 microliters) to appropriate wells;

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4. Incubate plate at 40 °C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

5 All compounds were tested in triplicate.

Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured  
10 at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC<sub>50</sub> values were determined. Typically, the IC<sub>50</sub> values (see, Table I,  
15 below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405  
20 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC<sub>50</sub> values. IC<sub>50</sub> were determined by  
25 plotting log concentration versus inhibition values in the range from 10-90% inhibition.

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Results of Human Secreted Phospholipase A<sub>2</sub> Inhibition  
Tests

Table

Compound No. from Examples 3-10	Inhibition of human secreted PLA <sub>2</sub> IC <sub>50</sub> ± mean deviation (3-4 tests) (nM)
1	49
2A	529
2B	533
2C	82
2D	874
2E	666
2F	698
2G	283
2H	166
3A	71
3B	59
3C	28
3D	132
3E	64
3F	44.7
3G	36.4
3H	25.1

5        The compound of Example 1 is highly active in  
inhibiting sPLA<sub>2</sub>.

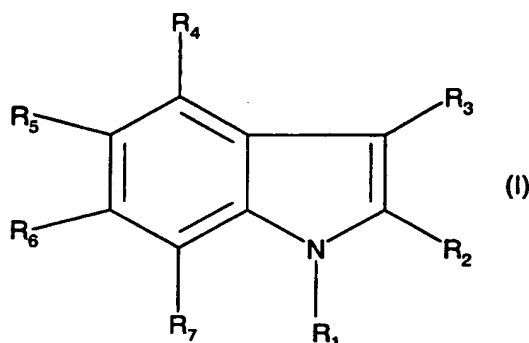
While the present invention has been illustrated  
above by certain specific embodiments, it is not intended  
10    that these specific examples should limit the scope of the  
invention as described in the appended claims.

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WE CLAIM:

1. An indole compound represented by the formula  
(I), or a pharmaceutically acceptable salt, solvate, or  
5 prodrug derivative thereof;



wherein ;

- 10  $R_1$  is selected from groups (a), (b), and (c)

wherein;

(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

- 15 (b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

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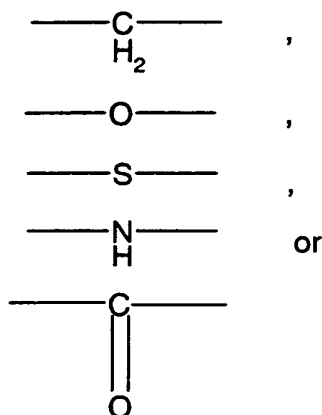
(c) is the group  $-(L_1)-R_{11}$ ; where,  $-(L_1)-$  is a divalent linking group of 1 to 8 atoms and where  $R_{11}$  is a group selected from (a)

or (b);

5  $R_2$  is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

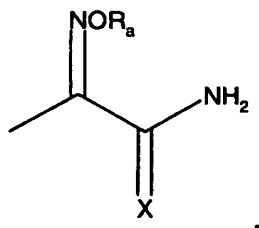
$R_3$  is  $-(L_3)-Z$ , where  $-(L_3)-$  is a divalent linker group selected from a bond or a divalent group selected from:

10



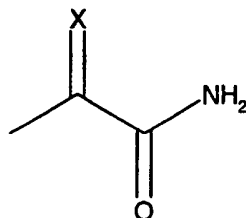
and Z is selected from a group represented by the formulae,

15



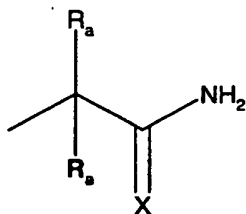
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or

5



wherein, X is oxygen or sulfur; and  $R_a$  is selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, aralkyl and -CN;

10  $R_4$  is the group,  $-(L_C)-(acylamino\ acid\ group)$ ; wherein  $-(L_C)-$ , is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

$R_5$  is selected from hydrogen, a non-interfering substituent, or the group,  $-(L_A)-(acidic\ group)$ ; wherein  
15  $-(L_A)-$ , is an acid linker having an acid linker length of 1 to 8;

$R_6$  and  $R_7$  are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s),



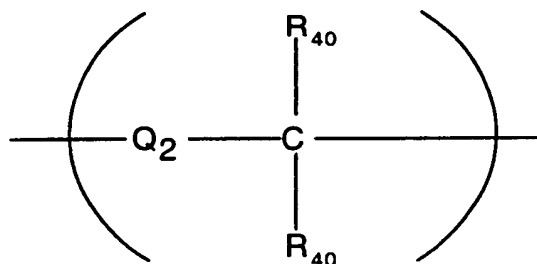
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heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

2. The compound of claim 1 wherein R<sub>2</sub> is  
5 hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, -O-(C<sub>1</sub>-C<sub>3</sub> alkyl),  
-S-(C<sub>1</sub>-C<sub>3</sub> alkyl), C<sub>3</sub>-C<sub>4</sub> cycloalkyl, -CF<sub>3</sub>, halo, -NO<sub>2</sub>, -  
CN, or -SO<sub>3</sub>.

3. The compound of Claim 1 wherein the acylamino  
10 acid linker group,  $-(L_C)-$ , for  $R_4$  is selected from a  
group represented by the formula;

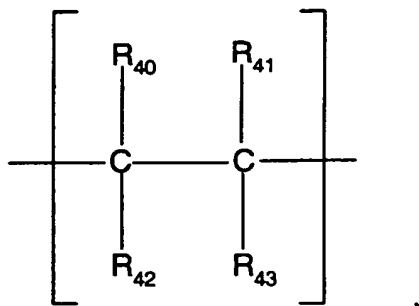
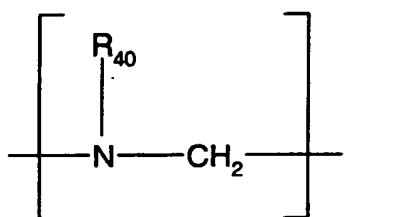
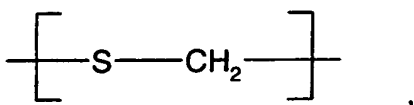
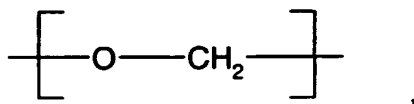


15 where Q<sub>2</sub> is selected from the group -(CH<sub>2</sub>)-, -O-, -NH-,  
-C(O)-, and -S-, and each R<sub>40</sub> is independently selected  
from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub>  
alkoxy, aralkyl, and halo.

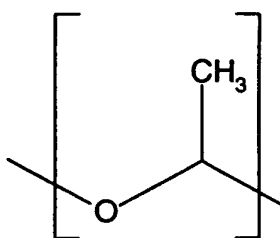
20           4.    The compound of Claim 1 wherein the acylamino  
acid linker group,  $-(L_c)-$ , for  $R_4$  selected from  $-(L_c)-$   
is a divalent group selected from,

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or



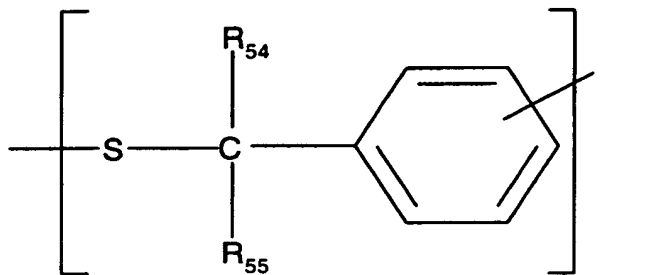
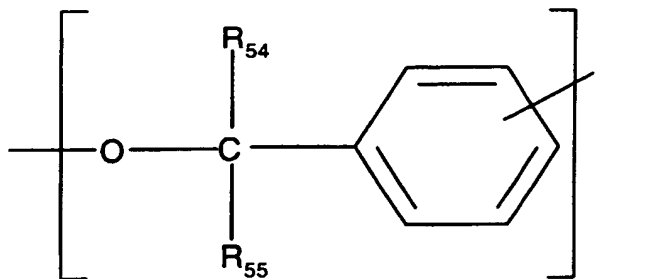
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where  $\text{R}_{40}$ ,  $\text{R}_{41}$ ,  $\text{R}_{42}$ , and  $\text{R}_{43}$  are each independently selected from hydrogen,  $\text{C}_1$ - $\text{C}_8$  alkyl.

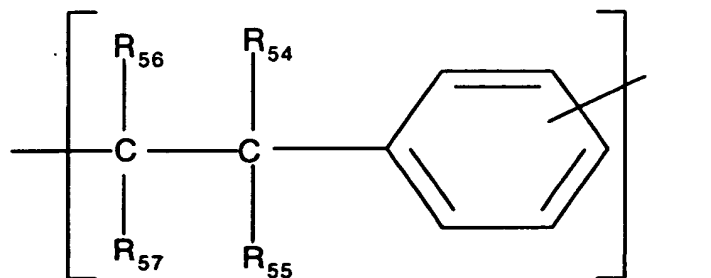
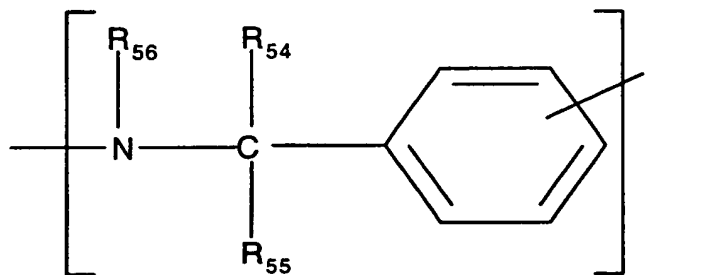
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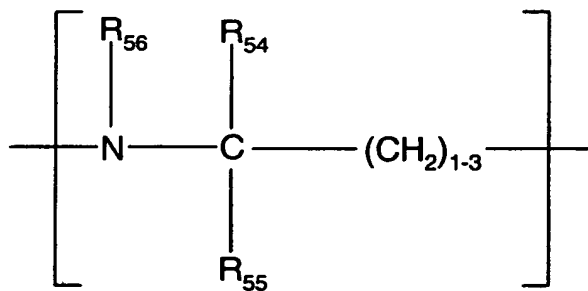
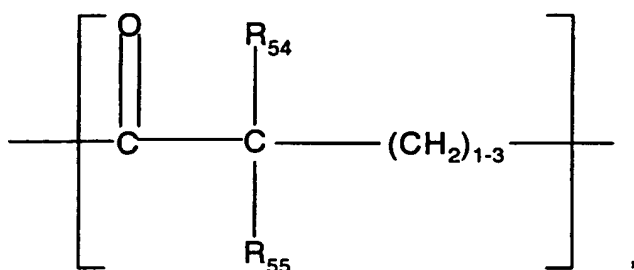
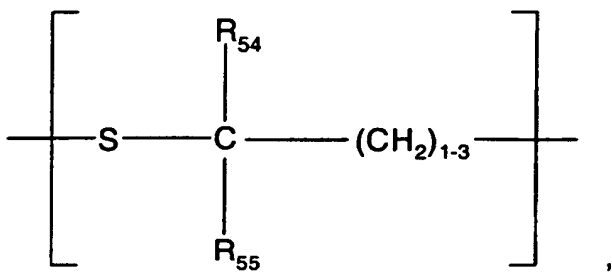
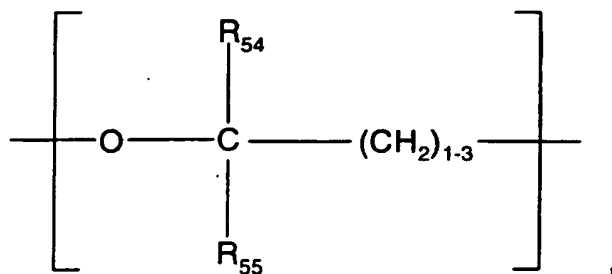
5. The compound of Claim 1 wherein the acid linker,  $-(L_a)-$ , for  $R_5$  is selected from a group represented by the formulae consisting of;



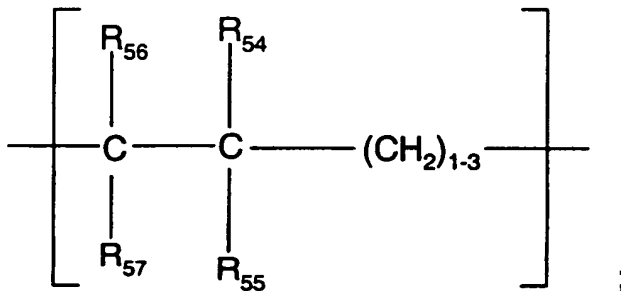
5



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and



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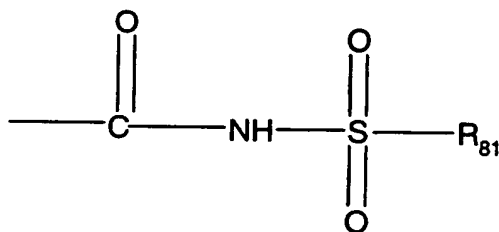
wherein R<sub>54</sub>, R<sub>55</sub>, R<sub>56</sub> and R<sub>57</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, or halo.

- 5            6. The compound of claim 1 wherein R<sub>5</sub> is the group, -(L<sub>a</sub>)-(acidic group) and wherein the (acidic group) is selected from the group:

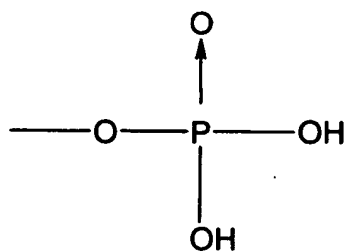
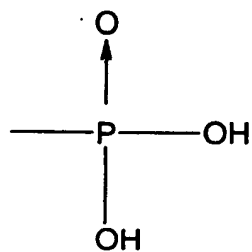
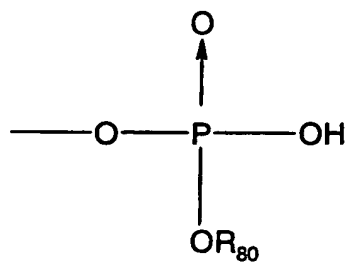
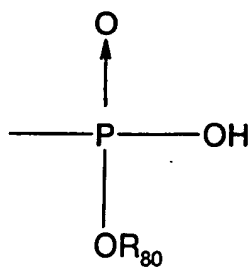
-5-tetrazolyl,

10

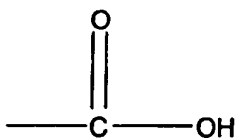
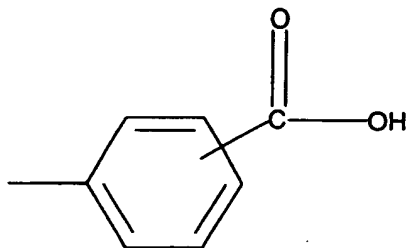
-SO<sub>3</sub>H,



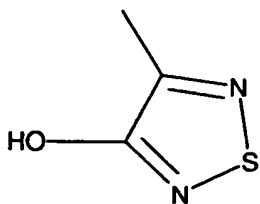
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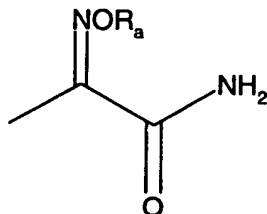


or



where  $R_{80}$  is a metal or  $C_1$ - $C_8$  alkyl and  $R_{81}$  is an organic substituent or  $-CF_3$ .

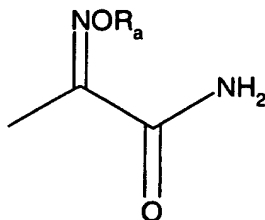
- 5            7. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



and the linking group  $-(L_3)-$  is a bond; and  $R_a$  is  
 10 hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

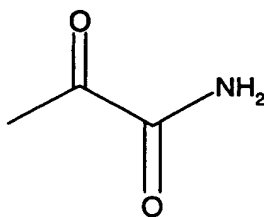
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8. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



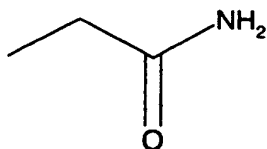
and the linking group  $-(L_3)-$  is a bond; and  $R_a$  is  
5 hydrogen.

9. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



10 and the linking group  $-(L_3)-$  is a bond.

10. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



15 and the linking group  $-(L_3)-$  is a bond.

11. The compound of Claim 1 wherein, for  $R_6$  the non-interfering substituent is hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl,



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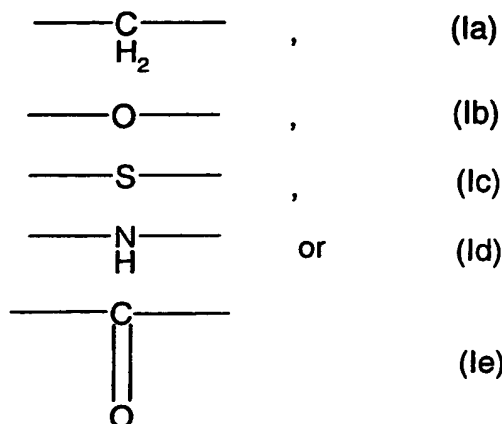
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C2-C8 alkenyl, C2-C8 alkynyl, C7-C12 aralkyl, C7-C12 alkaryl, C3-C8 cycloalkyl, C3-C8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C1-C8 alkoxy, C2-C8 alkenyloxy, C2-C8 alkynyloxy, C2-C12 alkoxyalkyl, C2-C12 alkoxyalkyloxy, C2-C12 alkylcarbonyl, C2-C12 alkylcarbonylamino, C2-C12 alkoxyamino, C2-C12 alkoxyaminocarbonyl, C1-C12 alkylamino, C1-C6 alkylthio, C2-C12 alkylthiocarbonyl, C1-C8 alkylsulfinyl, C1-C8 alkylsulfonyl, C2-C8 haloalkoxy, C1-C8 haloalkylsulfonyl, C2-C8 haloalkyl, C1-C8 hydroxyalkyl, -C(O)O(C1-C8 alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C1-C8 alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH<sub>2</sub>)<sub>n</sub>-CO<sub>2</sub>H, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO<sub>3</sub>H, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

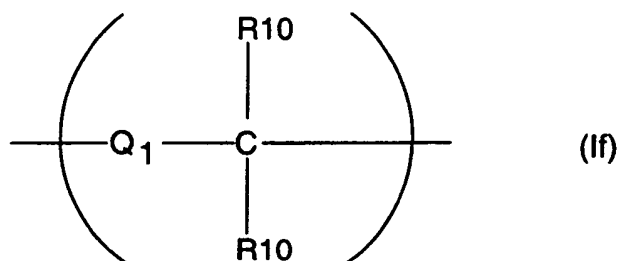
12. The compound of Claim 1 wherein for R<sub>1</sub> the divalent linking group -(L<sub>1</sub>)- is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):

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or



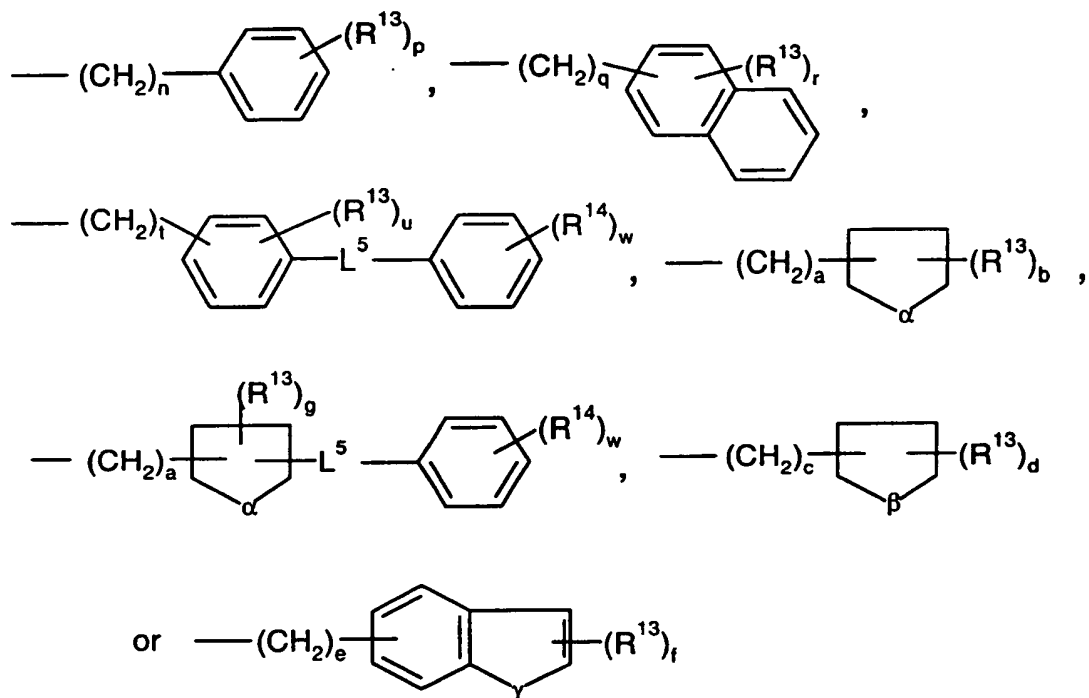
- 5 where  $Q_1$  is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and  $R_{10}$  is independently -H,  $C_{1-8}$  alkyl,  $C_{1-8}$  haloalkyl or  $C_{1-8}$  alkoxy.

13. The compound of claim 1 wherein the linking  
 10 group  $-(L_1)-$  of  $R_1$  is  $-(CH_2)-$  or  $-(CH_2-CH_2)-$ .

14. The compound of claim 1 wherein the linking  
 group  $-(L_{11})-$  of  $R_{11}$  is a bond and  $R_{11}$  is  $-(CH_2)_m-R^{12}$   
 wherein  $m$  is an integer from 1 to 6, and  $R^{12}$  is a group  
 15 represented by the formula:

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wherein a, c, e, n, q, and t are independently an integer from 0 to 2,  $R^{13}$  and  $R^{14}$  are independently selected from a halogen,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$

5 alkyloxy,  $C_1$  to  $C_8$  alkylthio, aryl, heteroaryl, and  $C_1$  to  $C_8$  haloalkyl,  $\alpha$  is an oxygen atom or a sulfur atom,  $L^5$  is a bond,  $-(CH_2)_v-$ ,

$-C=C-$ ,  $-CC-$ ,  $-O-$ , or  $-S-$ , v is an integer from 0 to 2,  $\beta$  is  $-CH_2-$  or  $-(CH_2)_2-$ ,  $\gamma$  is an oxygen atom or a sulfur

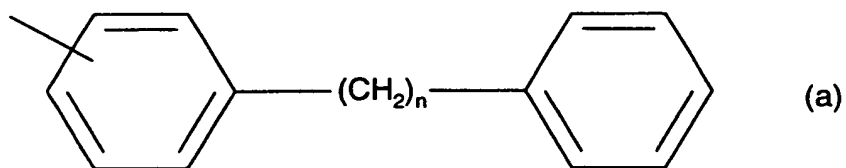
10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group

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consisting of C<sub>1</sub> to C<sub>6</sub> alkyl, C<sub>1</sub> to C<sub>8</sub> alkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyl, aryl, and a halogen..

15. The compound of claim 1 wherein for R<sub>1</sub> the  
5 group R<sub>11</sub> is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl, 10 diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a):



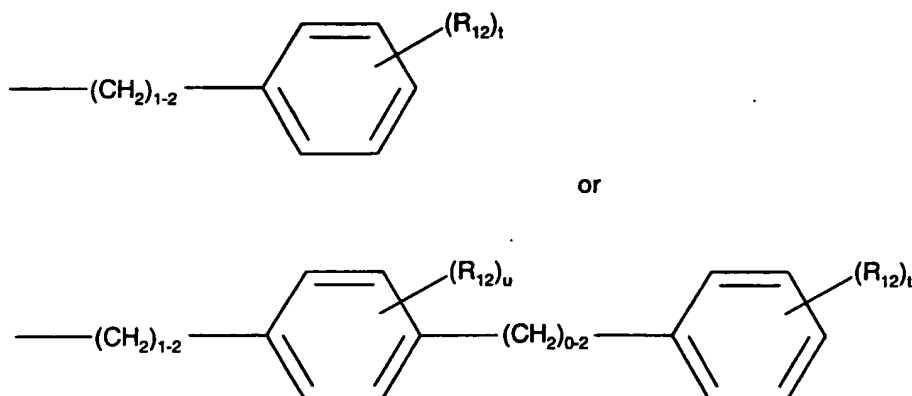
where n is a number from 1 to 8.

15

16. The compound of Claim 12 wherein for R<sub>1</sub> the combined group  $-(L_1)-R_{11}$  is selected from the groups;

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where  $R_{12}$  is a radical independently selected from halo,  $C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy,  $-S-(C_1-C_{10} \text{ alkyl})$ , and  $C_1$ -  
 5  $C_{10}$  haloalkyl,  $C_1$ - $C_{10}$  hydroxyalkyl and  $t$  is a number from 0 to 5 and  $u$  is a number from 0 to 4.

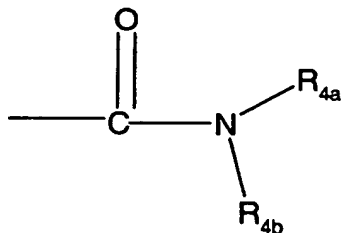
17. The compound of claim 1 wherein for  $R_1$  the radical  $R_{11}$  is a substituted or unsubstituted  
 10 heterocyclic radical selected from pyrrolyl, pyrrolodinyll, piperidinyll, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl,  
 15 dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1,2-A)pyridinyll, benzotriazolyl, anthranilyll, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyll, pyridinyll, dipyridylyll, phenylpyridinyll, benzylpyridinyll, pyrimidinyll, phenylpyrimidinyll,  
 20 pyrazinyll, 1,3,5-triazinyll, quinolinyll, phthalazinyll,

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quinazolinylmorpholino, thiomorpholino, homopiperazinyl,  
tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-  
dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,  
tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-  
5 dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny,  
hexamethyleneiminium, heptamethyleneiminium, piperazinyl  
or quinoxaliny.

18. The compound of claim 1 wherein  $R_4$  is the  
10 group,  $-(L_C)-(acylamino\ acid\ group)$  and wherein the  
(acylamino acid group) is:

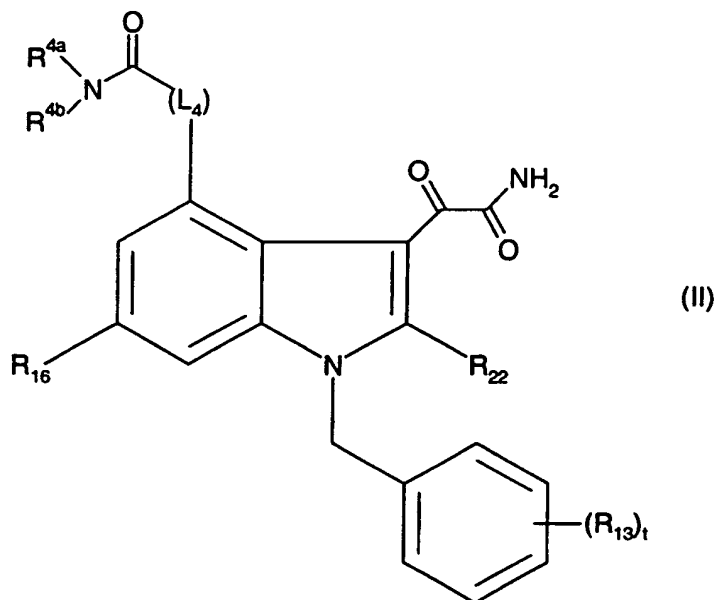


15 and  $R^{4a}$  is selected from the group consisting of H,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, heteroaryl and aryl; and wherein  
 $NR^{4b}$  is an amino acid residue with the nitrogen atom being  
part of the amino group of the amino acid.

20 19. An indole compound represented by the  
formula (II), or a pharmaceutically acceptable salt,  
solvate, or prodrug derivative thereof;

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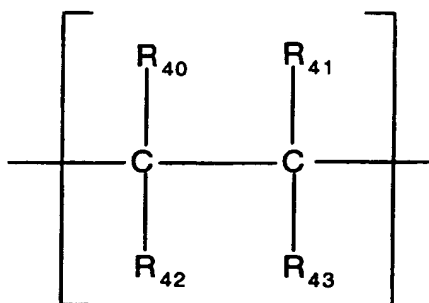
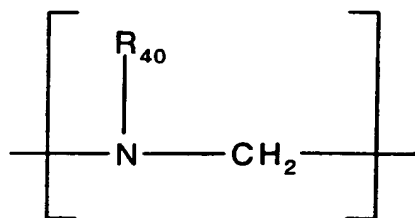
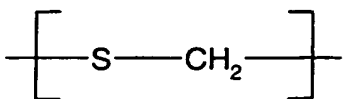
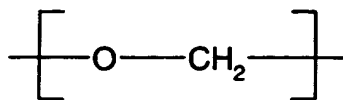
5 wherein ;

$R_{22}$  is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF<sub>3</sub>, -Cl, -Br, or -O-CH<sub>3</sub>;

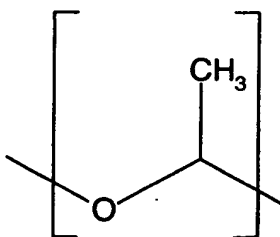
$R^{4a}$  is hydrogen; and

10  $NR^{4b}$  is an amino acid residue with the nitrogen atom being part of the amino group of the amino acid, and -  
(L<sub>C</sub>)- is a divalent group selected from;

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or



5 where  $\text{R}_{40}$ ,  $\text{R}_{41}$ ,  $\text{R}_{42}$ , and  $\text{R}_{43}$  are each independently selected from hydrogen or  $\text{C}_1$ - $\text{C}_8$  alkyl.

$\text{R}_{16}$  is selected from hydrogen,  $\text{C}_1$ - $\text{C}_8$  alkyl,  $\text{C}_1$ - $\text{C}_8$  alkoxy,  $\text{C}_1$ - $\text{C}_8$  alkylthio  $\text{C}_1$ - $\text{C}_8$  haloalkyl,  $\text{C}_1$ - $\text{C}_8$   
 10 hydroxyalkyl, and halo.



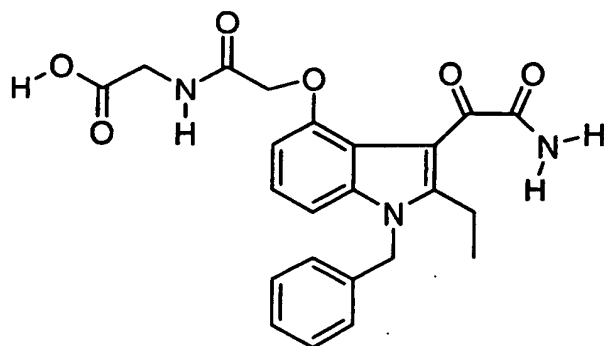
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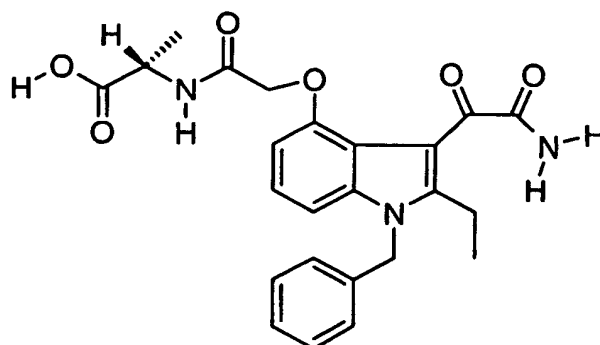
$R_{13}$  is selected from hydrogen and C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>8</sub> alkyl), C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, phenyl, halophenyl, and halo, and t is an integer from 0 to 5.

5

20. An indole compound represented by the formulae (C1), (C2), (C3), (C4), (C5), (C6), (C7), (C8), (C9), (C10) or (C11);



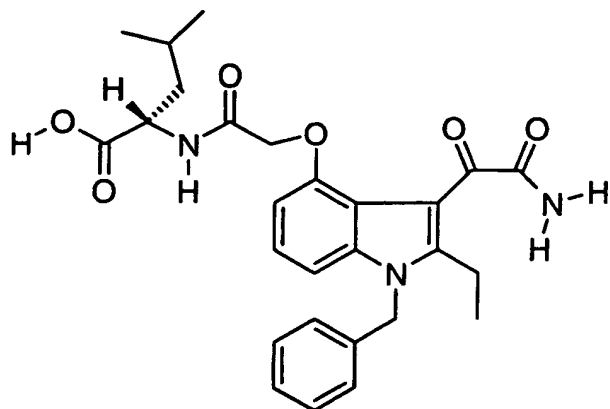
(C1),



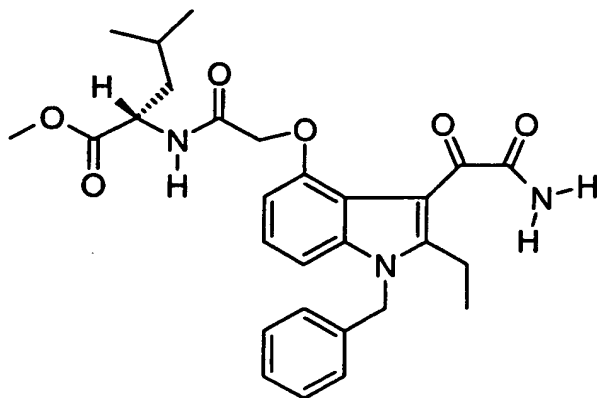
(C2),

10

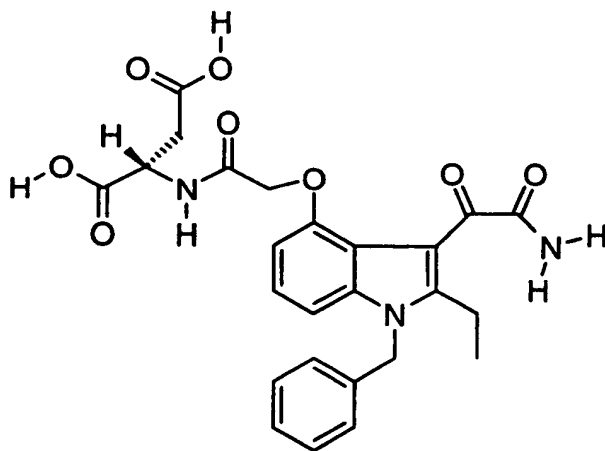
-130-



(C3) ,

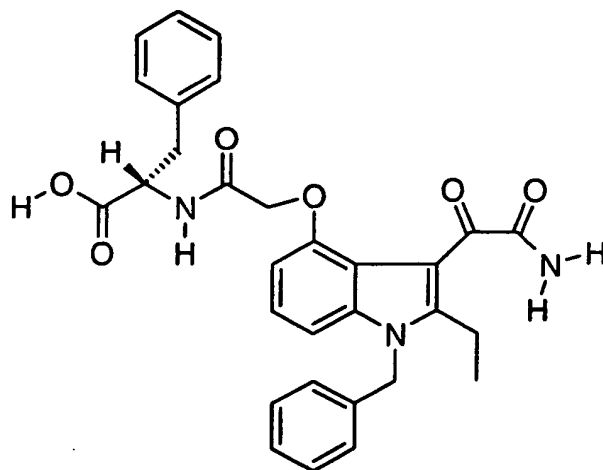


(C4) ,

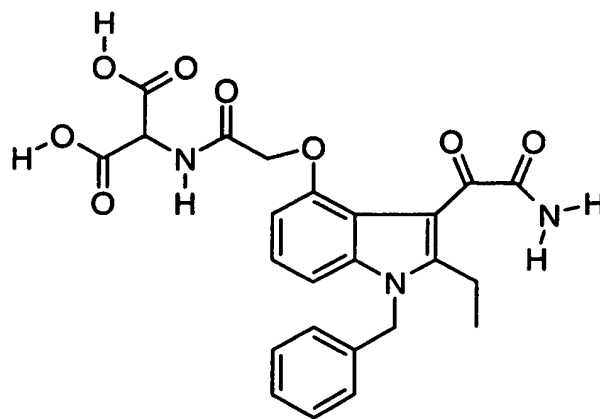


(C5) ,

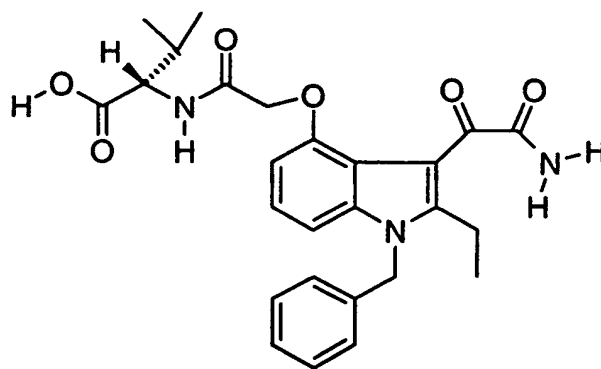
-131-



(C6) ,

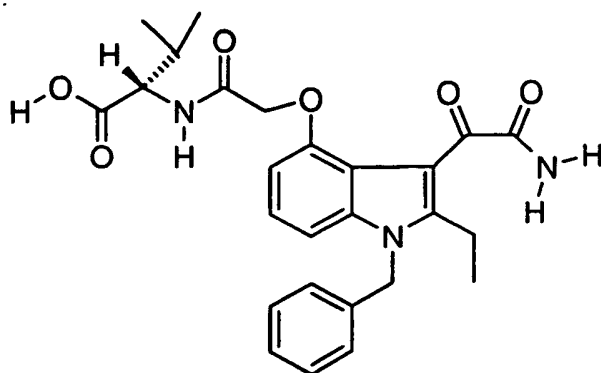


(C7) ,

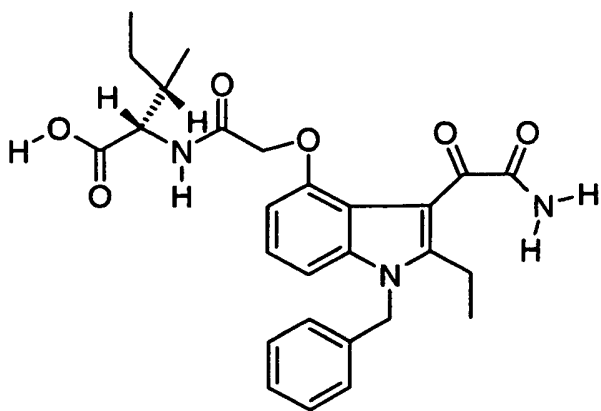


(C8) ,

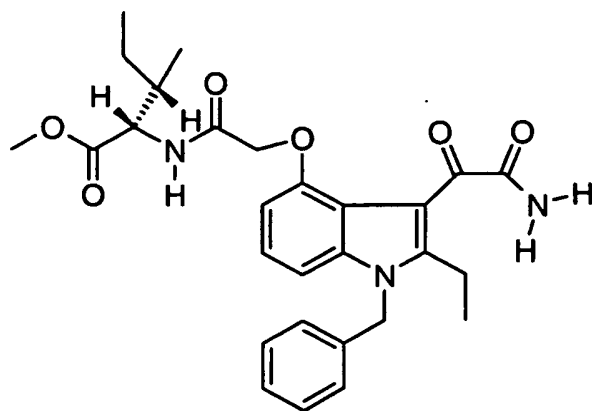
-132-



(C9) ,



(C10) and



(C11)

or pharmaceutically acceptable salts or prodrugs thereof.

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20. A compound of claim 1 selected from the group consisting of:

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

5        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine;

10        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

15        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

20        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

5        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

10       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

15       [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
indol-4-yl]oxy]acetamido]malonic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-valine;

20       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-valine;

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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

5        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

21. A pharmaceutical formulation comprising a indole  
compound as claimed in claim 1 together with a  
10 pharmaceutically acceptable carrier or diluent therefor.

22. A method of inhibiting sPLA<sub>2</sub> mediated release  
of fatty acid which comprises contacting sPLA<sub>2</sub> with a  
therapeutically effective amount of indole compound as  
15 claimed in claim 1.

23. A method of treating a mammal, including a  
human, to alleviate the pathological effects of  
Inflammatory Diseases; wherein the method comprises  
20 administration to said mammal of at least one indole  
compound as claimed in Claim 1 in a pharmaceutically  
effective amount.

24. A compound of claim 1 or a pharmaceutical  
25 formulation containing an effective amount of the

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compound of claim 1 in treatment of Inflammatory Diseases.

25. A compound of claim 1 or a pharmaceutical  
5 formulation containing an effective amount of the  
compound of claim 1 for use as an inhibitor for  
inhibiting sPLA<sub>2</sub> mediated release of fatty acid.

26. Use of a pharmaceutical composition comprising  
10 sPLA<sub>2</sub> inhibitor compounds according to Claim 1 and  
mixtures thereof for the manufacture of a medicament for  
the therapeutic treatment of Inflammatory Diseases.



## SPLA2 INHIBITORS

### Field of the Invention

This invention relates to novel indole compounds  
5 useful for Inflammatory Diseases.

### Background of the Invention

The structure and physical properties of human non-pancreatic secretory phospholipase A<sub>2</sub> (hereinafter  
10 called, "sPLA<sub>2</sub>") has been thoroughly described in two articles, namely, "Cloning and Recombinant Expression of Phospholipase A<sub>2</sub> Present in Rheumatoid Arthritic Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski, Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.;  
15 Kloss, Jean; and Johnson, Lorin K.; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5335-5338, 1989; and "Structure and Properties of a Human Non-pancreatic Phospholipase A<sub>2</sub>" by Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes,  
20 Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard, Richard; and Pepinsky, R. Blake; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5768-5775, 1989; the disclosures of which are incorporated herein by reference.

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It is believed that sPLA<sub>2</sub> is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA<sub>2</sub> mediated release  
5 of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA<sub>2</sub>; such as sepsis or rheumatoid arthritis.

10 It is desirable to develop new compounds and treatments for sPLA<sub>2</sub> induced diseases.

#### Summary of the Invention

This invention provides novel indole compounds  
15 having potent and selective effectiveness as inhibitors of mammalian sPLA<sub>2</sub>.

This invention is also the use of novel indole compounds useful in the treatment and prevention of  
20 Inflammatory Diseases.

This invention is also the use of novel of indole compounds to inhibit mammalian sPLA<sub>2</sub> mediated release of fatty acids.

25

-3-

This invention is also a pharmaceutical composition containing any of the indole compounds of the invention.

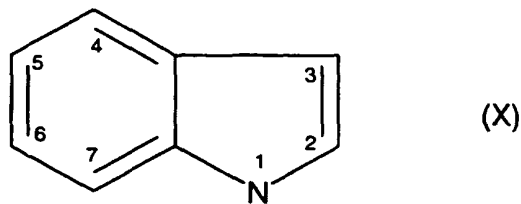
5   **I.   Definitions:**

          The term, "Inflammatory Diseases" refers to diseases such as inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, 10 allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, 15 enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, 20 arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, 25 bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing),

-4-

miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated  
5 with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis,  
10 or relapsing polychondritis and related diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of the compound of formula I in an amount sufficient to inhibit  
sPLA<sub>2</sub> mediated release of fatty acid and to thereby  
15 inhibit or prevent the arachidonic acid cascade and its deleterious products.

The term, "indole nucleus" refers to a nucleus (having numbered positions) with the structural  
20 formula (X):



The indole compounds of the invention employ certain defining terms as follows:

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The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary  
5 butyl, sec-butyl, n-pentyl, and n-hexyl.

The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated  
10 number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group  
15 containing only carbon and hydrogen.

The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or  
20 unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrrolodiny, piperidinyl, furanyl,  
25 thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl,

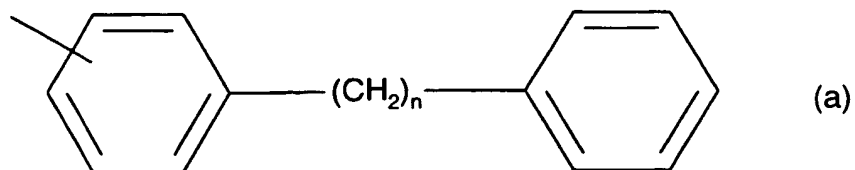
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indolyl, carbazolyl, norharmanyl, azaindolyl,  
benzofuranyl, dibenzofuranyl, dibenzothiophenyl,  
indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl,  
anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl,  
5 benzothiazolyl, purinyl, pyridinyl, dipyridyl,  
phenylpyridinyl, benzylpyridinyl, pyrimidinyl,  
phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl,  
phthalazinyl, quinazolinyl, morpholino, thiomorpholino,  
homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl,  
10 oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,  
tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-  
dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidyl,  
hexamethyleneiminium, heptamethyleneiminium, piperazinyl  
and quinoxalinyl.

15

The term, "carbocyclic radical" refers to radicals  
derived from a saturated or unsaturated, substituted or  
unsubstituted 5 to 14 membered organic nucleus whose ring  
forming atoms (other than hydrogen) are solely carbon  
20 atoms. Typical carbocyclic radicals are cycloalkyl,  
cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl,  
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,  
indenyl, stilbenyl, terphenyl, diphenylethylenyl,  
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,  
25 biphenyl, bibenzyl and related bibenzyl homologues  
represented by the formula (a):

-7-



where n is a number from 1 to 8.

5           The term, "non-interfering substituent", refers to radicals suitable for substitution at positions 4,5,6 and/or 7 of the indole nucleus and on other nucleus substituents (as hereinafter described for Formula I), and radicals suitable for substitution on the

10 heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>7</sub>-C<sub>12</sub> aralkyl, C<sub>7</sub>-C<sub>12</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>2</sub>-C<sub>8</sub>

15 alkenyloxy, C<sub>2</sub>-C<sub>8</sub> alkynyloxy, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyloxy, C<sub>2</sub>-C<sub>12</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>12</sub> alkylcarbonylamino, C<sub>2</sub>-C<sub>12</sub> alkoxyamino, C<sub>2</sub>-C<sub>12</sub> alkoxyaminocarbonyl, C<sub>1</sub>-C<sub>12</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>2</sub>-C<sub>12</sub> alkylthiocarbonyl, C<sub>1</sub>-C<sub>8</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>8</sub>

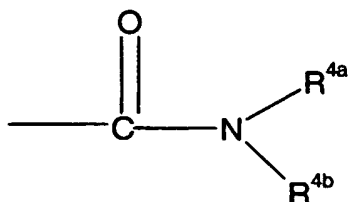
20 alkylsulfonyl, C<sub>2</sub>-C<sub>8</sub> haloalkoxy, C<sub>1</sub>-C<sub>8</sub> haloalkylsulfonyl, C<sub>2</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, -C(O)O(C<sub>1</sub>-C<sub>8</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C<sub>1</sub>-C<sub>8</sub> alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino,

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bromo, carbamyl, carboxyl, carbalkoxy,  $-(CH_2)_n-CO_2H$ ,  
chloro, cyano, cyanoguanidiny, fluoro, guanidino,  
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,  
iodo, nitro, phosphono,  $-SO_3H$ , thioacetal, thiocarbonyl,  
5 and carbonyl; where n is from 1 to 8 and R is  $C_1-C_8$   
alkyl.

The term, "organic substituent" refers to a  
monovalent radical consisting of carbon and hydrogen  
10 with or without oxygen, nitrogen, sulfur, halogen, or  
other elements. Illustrative organic substituents are  
 $C_1-C_8$  alkyl, aryl,  $C_7-C_{14}$  aralkyl,  $C_7-C_{14}$  alkaryl,  $C_3-C_8$   
cycloalkyl,  $C_1-C_8$  alkoxyalkyl and these groups  
substitued with halogen,  $-CF_3$ ,  $-OH$ ,  $C_1-C_8$  alkyl, amino,  
15 carbonyl, and  $-CN$ .

The term, "acylamino acid group" is represented by  
the formula:



20

wherein  $R^{4a}$  is selected from the group consisting of H,  
 $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, heteroaryl and aryl,  $-CF_3$ ;  
and wherein  $NR^{4b}$  is an amino acid residue of either a



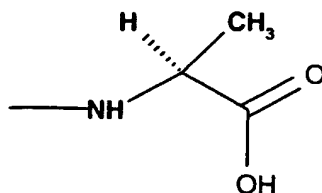
-9-

natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A typical amino acid is selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, 5 glycine, asparagine, cysteine, glutamine, glutamic acid, histidine, lysine, methionine, serine, threonine, tryptophan, tyrosine and derivatives thereof. Also contemplated within the definition of amino acid is *l*-proline, *d*-proline and derivatives thereof. Also 10 contemplated within the definition of amino acids are peptides, polypeptides and derivatives thereof.

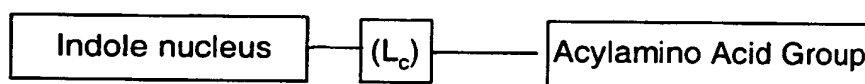
The term "substituted group" is an organic group substituted with one or more non-interfering 15 substituents.

The terms, "amino acid residue" refer to the portion of the amino acid group coupled at the nitrogen atom of the amino terminus. It is the amino acid less a 20 hydrogen atom from the amino terminus. It is further illustrated as used herein for the amino acid alanine attached at the nitrogen atom as shown below:

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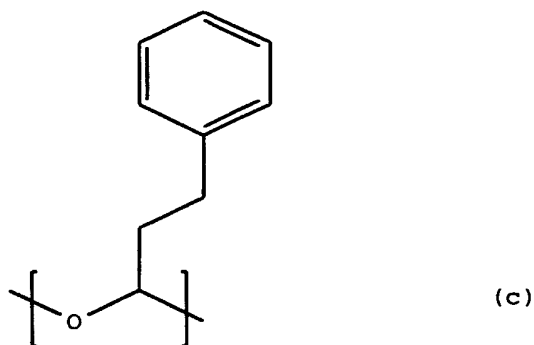
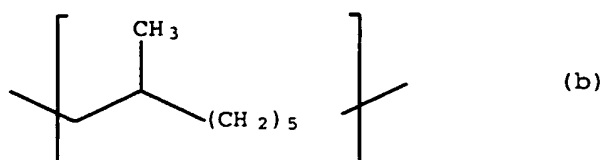
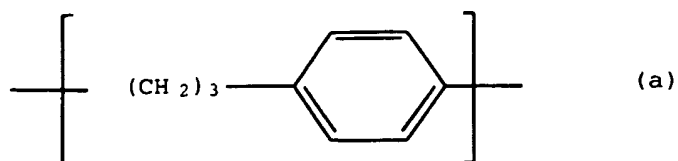


The words, "acylamino acid linker" refer to a divalent linking group symbolized as,  $-(L_C)-$ , which has the function of joining the 4 - position of the indole nucleus to an acylamino acid group in the general relationship:



The words, "acylamino acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group  $-(L_C)-$  that connects the 4 - position of the indole nucleus with the acylamino acid group. The presence of a carbocyclic ring in  $-(L_C)-$  counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of  $-(L_C)-$ . Illustrative acylamino acid linker groups are;

-11-



wherein, groups (a), (b) and (c) have acid linker lengths of 5, 7, and 2, respectively.

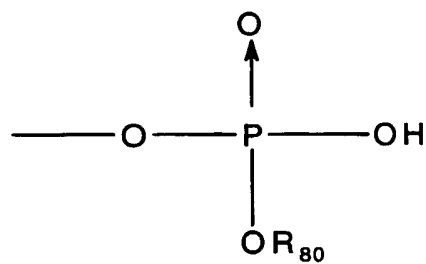
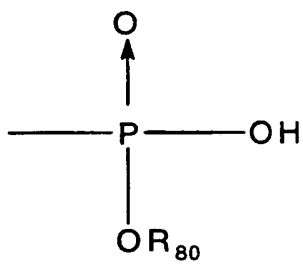
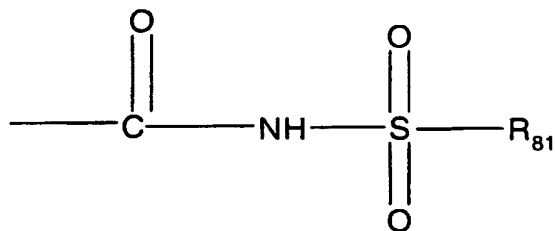
5

The term, "(acidic group)" means an organic group which when attached to an indole nucleus at position 5, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

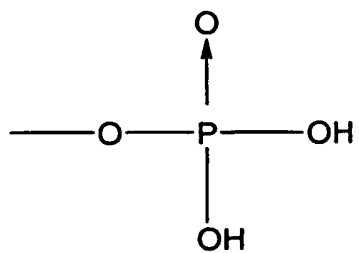
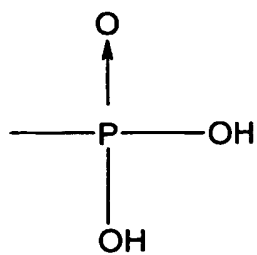
-5-tetrazolyl,

-SO<sub>3</sub>H,

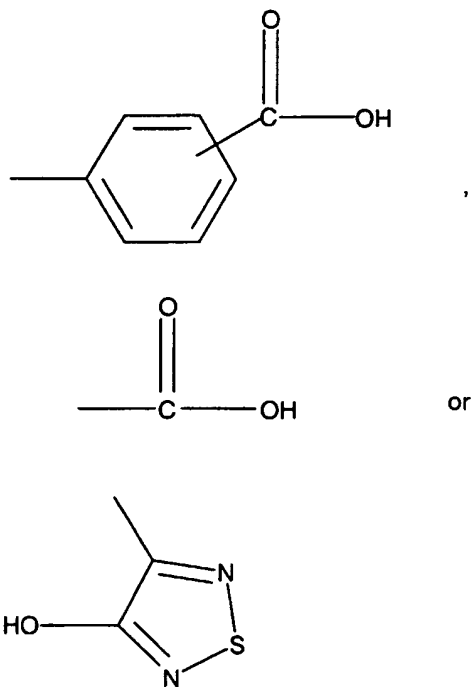
-12-



5

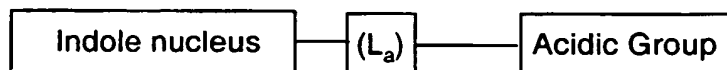


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where n is 1 to 8, R<sub>80</sub> is a metal or C<sub>1</sub>-C<sub>8</sub> and R<sub>81</sub>  
 5 is an organic substituent or -CF<sub>3</sub>.

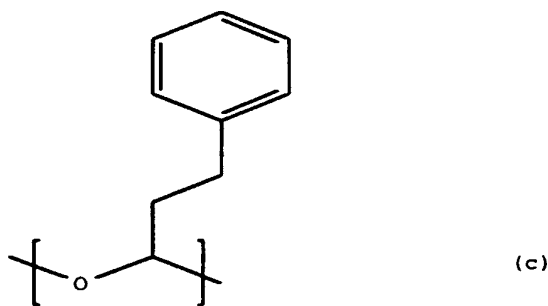
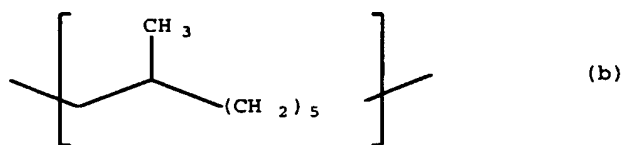
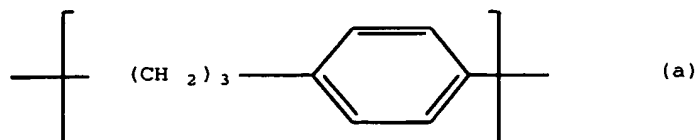
The words, "acid linker" refer to a divalent  
 linking group symbolized as, -(L<sub>a</sub>)-, which has the  
 function of joining the 5 position of the indole nucleus  
 10 to an acidic group in the general relationship:



The words, "acid linker length", refer to the number  
 of atoms (excluding hydrogen) in the shortest chain of the  
 15 linking group -(L<sub>a</sub>)- that connects the 5 position of the

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indole nucleus with the acidic group. The presence of a carbocyclic ring in  $-(L_a)-$  counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in  
 5 the acid linker counts as 2 atoms in calculating the length of  $-(L_a)-$ . Illustrative acid linker groups are;



10 wherein, groups (a), (b), and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "amine", includes primary, secondary and tertiary amines.

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The terms, "mammal" and "mammalian" include human and domesticated quadrupeds.

The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals,  $-\text{CH}_2-\text{CH}_2-$  and  $-\text{CH}_2-$ .

5

The term, "group containing 1 to 4 non-hydrogen atoms" refers to relatively small groups which form substituents at the 2 position of the indole nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as  $-\text{CF}_3$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{SO}_3$ ; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as  $-\text{CH}_3$ ,  $-\text{C}_2\text{H}_5$ , and  $-\text{CH}=\text{CH}_2$ .

20

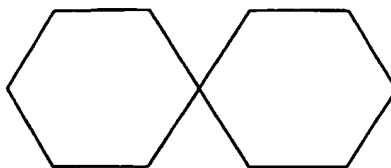
The term "oxime amide" means the radical,  
 $-\text{C}=\text{NOR}-\text{C}(\text{O})\text{NH}_2$

The term "thio-oxime amide" means the radical  
 $-\text{C}=\text{NOR}-\text{C}(\text{S})-\text{NH}_2$ .

The term "spiro[5.5]undecanyl" refers to the group represented by the formula;

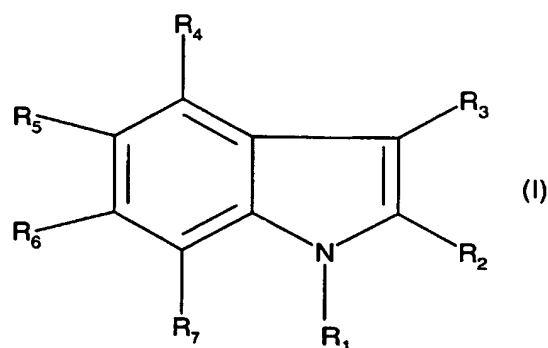
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## II. The amino acid 1H-indole Compounds of the Invention:

The present invention provides novel classes of  
5 indole compounds useful as sPLA2 inhibitors for the  
treatment of inflammation. Classes of indole compounds  
of this invention include indole glyoxylamide amino acid  
derivatives, indole-3-oxime amide amino acid derivatives  
and indole acetamide amino acid derivatives. The  
10 compounds of the invention have the general formula (I)  
or a pharmaceutically acceptable salt, solvate or  
prodrug thereof;



15

wherein ;

R<sub>1</sub> is selected from groups (a), (b), and (c)

wherein;



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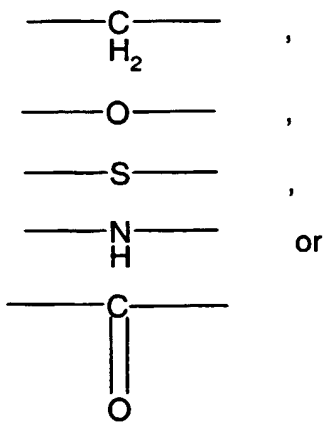
(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or  
5 more independently selected non-interfering substituents; or

(c) is the group  $-(L_1)-R_{11}$ ; where,  $-(L_1)-$  is a divalent linking group of 1 to 8 atoms and where  $R_{11}$  is a group selected from (a) or (b);

10  $R_2$  is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

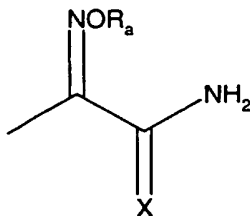
$R_3$  is  $-(L_3)-Z$ , where  $-(L_3)-$  is a divalent linker group selected from a bond or a divalent group selected from:



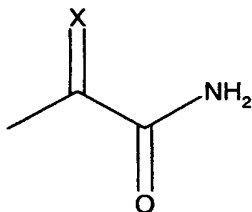
15

and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,

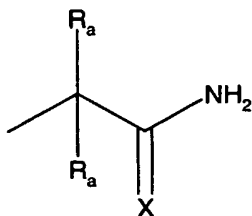
-18-



or



or



5

wherein X is oxygen or sulfur,  $R_a$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, aralkyl and -CN;

$R_4$  is the group,  $-(L_C)-(acylamino\ acid\ group)$ ;

10 wherein  $-(L_C)-$ , is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

$R_5$  is selected from hydrogen, a non-interfering substituent, or the group,  $-(L_A)-(acidic\ group)$ ; wherein  $-(L_A)-$ , is an acid linker having an acid linker length

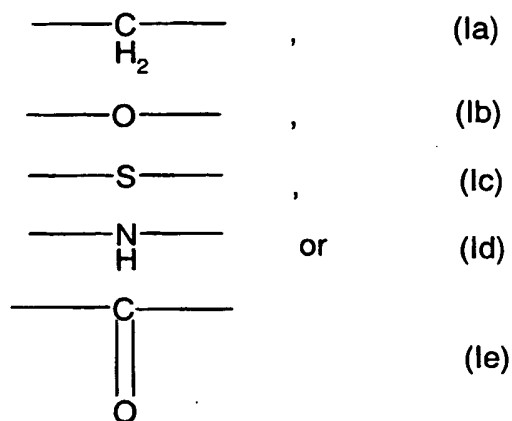
15 of 1 to 8.

-19-

R<sub>6</sub> and R<sub>7</sub> are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

**Preferred Subgroups of Compounds of Formula (I):**  
**Preferred R<sub>1</sub> substituents:**

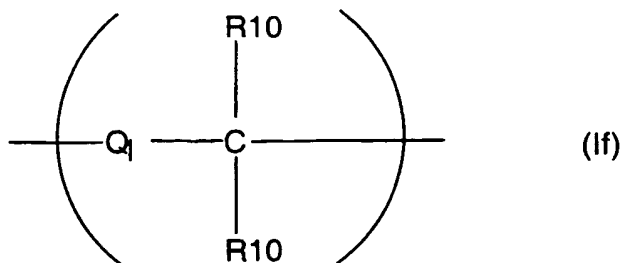
A preferred subclass of compounds of formula (I) are those where for R<sub>1</sub> the divalent linking group -(L<sub>1</sub>)- is a group represented by any one of the following formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



15

or

-20-



where  $Q_1$  is a bond or any of the divalent groups (Ia), (Ib), (Ic), (Id), (Ie), and (If) and each  $R_{10}$  is

5 independently hydrogen,  $C_{1-8}$  alkyl,  $C_{1-8}$  haloalkyl or  $C_{1-8}$  alkoxy.

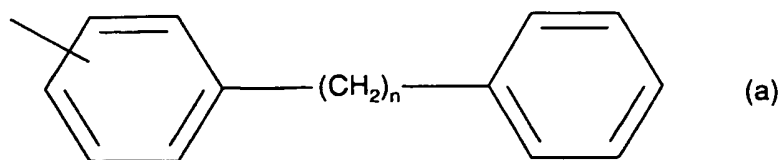
Particularly preferred as the linking group  $-(L_1)-$  of  $R_1$  is an alkylene chain of 1 or 2 carbon atoms, namely,

10  $-(CH_2)-$  or  $-(CH_2-CH_2)-$ .

The preferred group for  $R_{11}$  is a substituted or unsubstituted group selected from the group consisting of  $C_5-C_{14}$  cycloalkyl,  $C_5-C_{14}$  cycloalkenyl, phenyl, naphthyl,

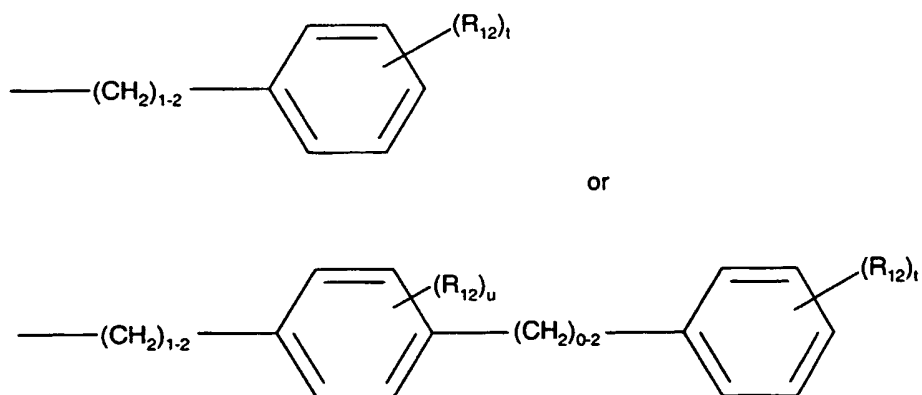
15 norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a);

-21-



where  $n$  is a number from 1 to 8.

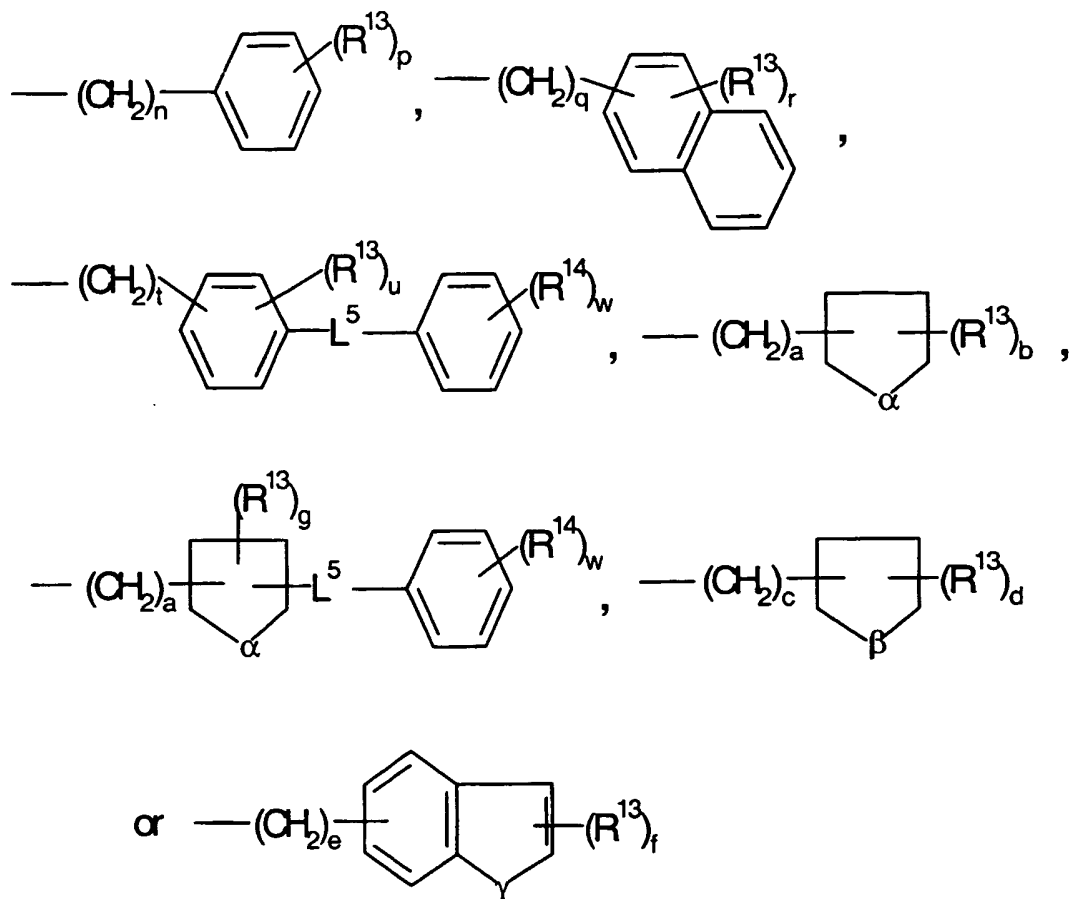
Particularly preferred are compounds wherein for  $R_1$   
 5 the combined group  $-(L_1)-R_{11}$  is selected from the group  
 consisting of



where  $R_{12}$  is a radical independently selected from halo,  
 $C_1-C_8$  alkyl,  $C_1-C_8$  alkoxy,  $-S-(C_1-C_8 \text{ alkyl})$ ,  $-O-(C_1-C_8$   
 10 alkyl) and  $C_1-C_8$  haloalkyl where  $t$  is a number from 0 to  
 5 and  $u$  is a number from 0 to 4 is the group  $-(L_1)-R_{11}$ ;  
 where,  $-(L_1)-$  is a divalent linking group of 1 to 8  
 atoms and where  $R_{11}$  is a group selected from (a) or (b).

15 Preferred for  $R_{11}$  is  $-(CH_2)_m-R^{12}$  wherein  $m$  is an  
 integer from 1 to 6, and  $R^{12}$  is (d) a group represented by  
 the formula:

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wherein a, c, e, n, q, and t are independently an integer from 0 to 2,  $R^{13}$  and  $R^{14}$  are independently selected from a halogen,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$

5 alkyloxy,  $C_1$  to  $C_8$  alkylthio, aryl, heteroaryl, and  $C_1$  to  $C_8$  haloalkyl,  $\alpha$  is an oxygen atom or a sulfur atom,  $L^5$  is a bond,  $-(CH_2)_v-$ ,

$-C=C-$ ,  $-CC-$ ,  $-O-$ , or  $-S-$ , v is an integer from 0 to 2,  $\beta$  is  $-CH_2-$  or  $-(CH_2)_2-$ ,  $\gamma$  is an oxygen atom or a sulfur

10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer

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from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C<sub>1</sub> to C<sub>6</sub> alkyl, C<sub>1</sub> to C<sub>8</sub> alkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyl, aryl, and a halogen.

5

**Preferred R<sub>2</sub> substituents:**

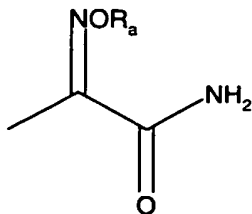
R<sub>2</sub> is preferably selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, -O-(C<sub>1</sub>-C<sub>3</sub> alkyl),

10 -S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>3</sub>-C<sub>4</sub> cycloalkyl -CF<sub>3</sub>, halo, -NO<sub>2</sub>, -CN, -SO<sub>3</sub>. Particularly preferred R<sub>2</sub> groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF<sub>3</sub>, -Cl, -Br, or -O-CH<sub>3</sub>.

15 **Preferred R<sub>3</sub> substituents:**

A preferred subclass of compounds of formula (I) are those wherein X is oxygen.

Another preferred subclass of compounds of  
20 formula (I) are those wherein Z is an oxime amide group.



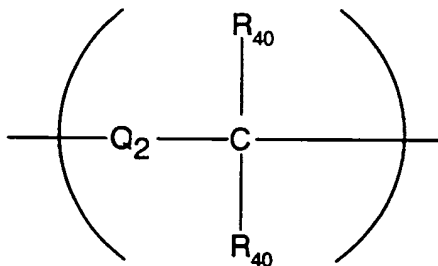
-24-

Also preferred are compounds of formula (I) wherein  $R_3$  is an oxime amide group and  $R_a$  is hydrogen, methyl or ethyl. For the group  $R_3$  it is preferred that the linking group  $-(L_3)-$  be a bond.

5

**Preferred  $R_4$  substituents:**

Another preferred subclass of compounds of formula (I) are those wherein  $R_4$  is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group,  $-(L_C)-$ , for  $R_4$  is selected from a group represented by the formula;

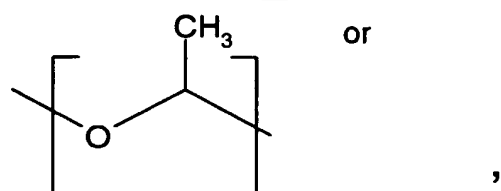
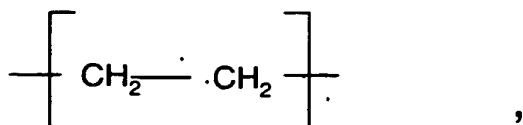
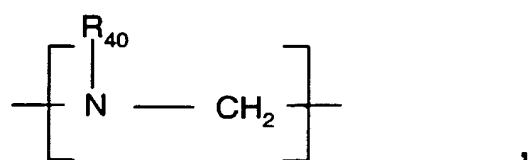
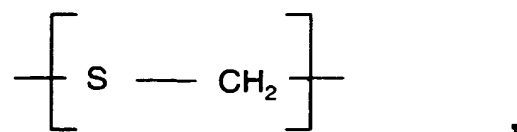
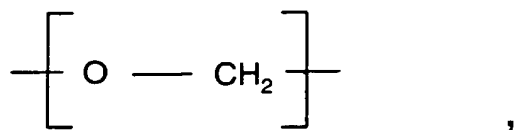


where  $Q_2$  is selected from the group  $-(CH_2)-$ ,  $-O-$ ,  $-NH-$ ,  $-C(O)-$ , and  $-S-$ , and each  $R_{40}$  is independently selected from hydrogen,  $C_1$ - $C_8$  alkyl, aryl,  $C_1$ - $C_8$  alkaryl,  $C_1$ - $C_8$  alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker,  $-(L_C)-$ , for  $R_4$  is selected from the specific groups;

20



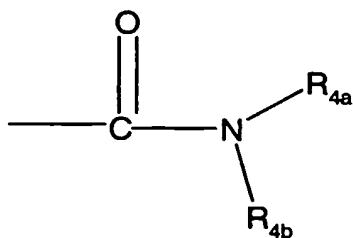
-25-



where  $\text{R}_{40}$  is hydrogen or  $\text{C}_1$  -  $\text{C}_8$  alkyl.

Preferred as the (acylamino acid group) in the group  $\text{R}_4$

5 is the group:



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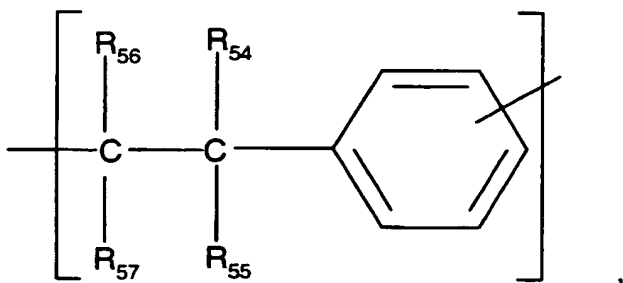
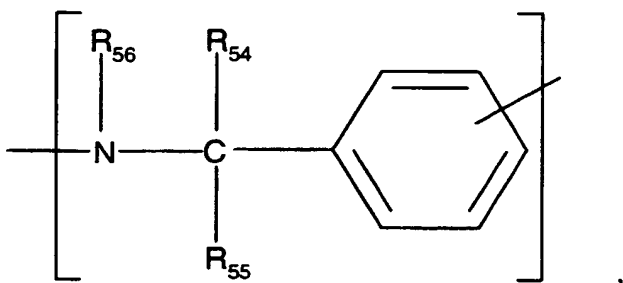
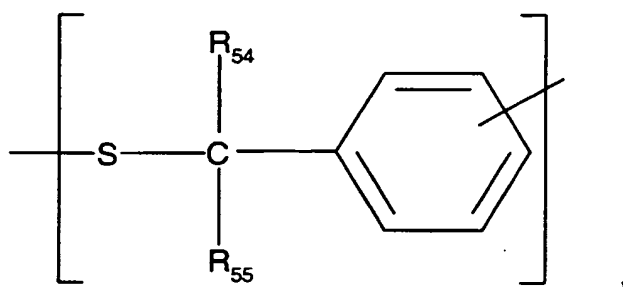
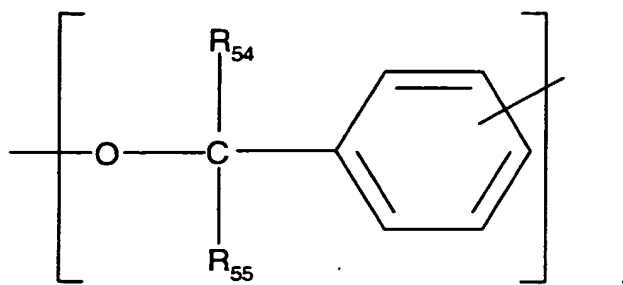
wherein R<sup>4a</sup> is selected from the group consisting of H,  
(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl; and  
wherein NR<sup>4b</sup> is an amino acid residue of either a natural  
or unnatural amino acid with the nitrogen atom being part  
5 of the amino group of the amino acid. A preferred R<sup>4a</sup>  
group is the group hydrogen (H). A preferred source of  
amino acid residue is the amino acid group selected from  
the group comprising isoleucine, valine, phenylalanine,  
aspartic acid, leucine, glycine and isomers and  
10 derivatives thereof. A salt or a prodrug derivative of  
the (acylamino acid group) is also a suitable substituent.

Particularly preferred are R<sup>4b</sup> groups that combine  
with the nitrogen atom to represent amino acid residues  
15 from the amino acid groups selected from: glycine,  
glycine methyl ester, L-alanine, L-alanine  
methylester, L-leucine, L-leucine methyl ester, L-  
aspartic acid, L-aspartic acid dimethyl ester, L-phenyl  
alanine, L-phenylalanine methyl ester, malonic acid,  
20 malonic acid dimethylester, L- valine, L-valine methyl  
ester, L-isoleucine, L-isoleucine methyl ester, or salt,  
and derivatives thereof.

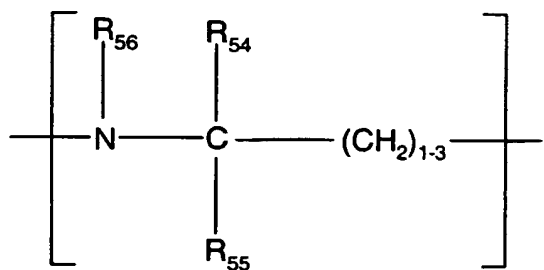
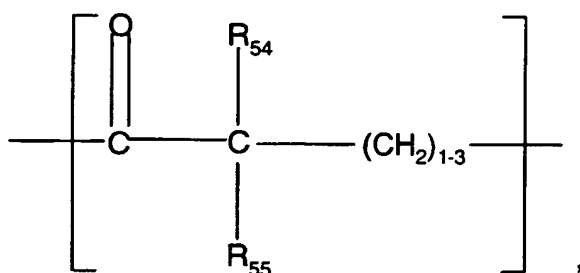
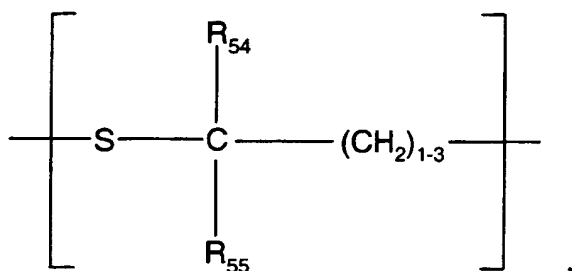
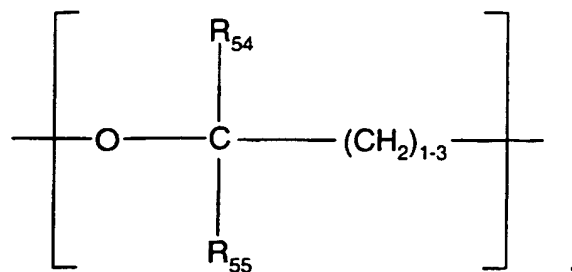
**Preferred R<sub>5</sub> Substituents:**

25 Preferred acid linker, -(L<sub>a</sub>)-, for R<sub>5</sub> is selected from  
the group consisting of;

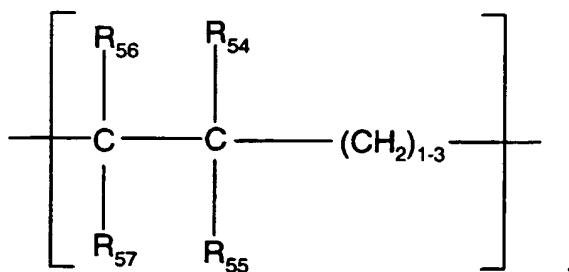
- 27 -



- 28 -



and



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wherein R<sub>54</sub>, R<sub>55</sub>, R<sub>56</sub> and R<sub>57</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, or halo. Preferred (acidic group) for R<sub>5</sub> is selected from the group consisting of -CO<sub>2</sub>H, -SO<sub>3</sub>H and

5 -P(O)(OH)<sub>2</sub>.

**Preferred R<sub>6</sub> and R<sub>7</sub> substituents:**

Another preferred subclass of compounds of formula (I) are those wherein for R<sub>6</sub> and R<sub>7</sub> the non-

10 interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C<sub>4</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>7</sub>-C<sub>12</sub> aralkyl, C<sub>7</sub>-C<sub>12</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub>

15 alkenyloxy, C<sub>2</sub>-C<sub>6</sub> alkynyloxy, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyloxy, C<sub>2</sub>-C<sub>12</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>12</sub> alkylcarbonylamino, C<sub>2</sub>-C<sub>12</sub> alkoxyamino, C<sub>2</sub>-C<sub>12</sub> alkoxyaminocarbonyl, C<sub>1</sub>-C<sub>12</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>2</sub>-C<sub>12</sub> alkylthiocarbonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>

20 alkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, -C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH<sub>2</sub>)<sub>n</sub>-CO<sub>2</sub>H,

25 chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,

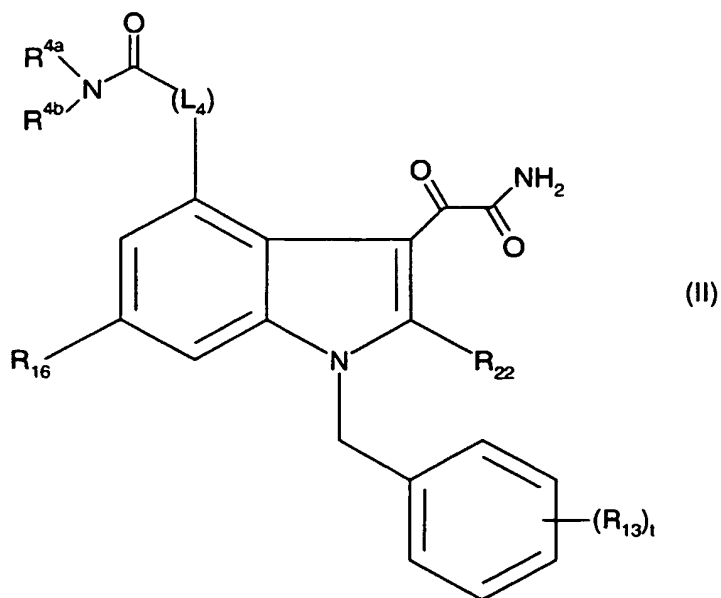
-30-

iodo, nitro, phosphono,  $-SO_3H$ , thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.

Most preferred as non-interfering substituents are  
5 methyl, ethyl, propyl, and isopropyl.

Preferred compounds of the invention are those having the general formula (II), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof;

10

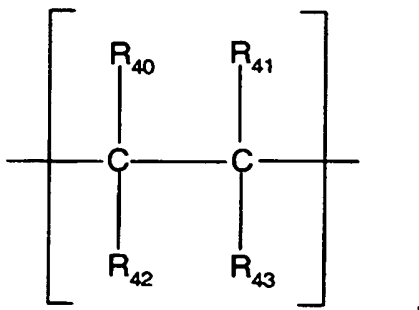
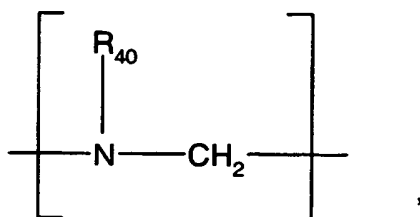
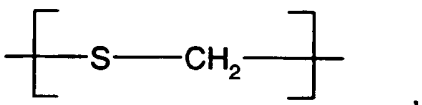
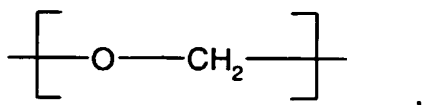


wherein ;

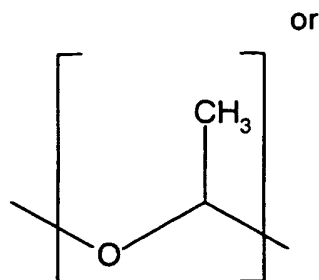
15  $R_{22}$  is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl,  $-F$ ,  $-CF_3$ ,  $-Cl$ ,  $-Br$ , or  $-O-CH_3$ ;

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wherein  $R^{4a}$  is selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl; and wherein  $NR^{4b}$  is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred  $R^{4a}$  group is the group hydrogen (H); and - (L<sub>4</sub>)- is a divalent group selected from;



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where  $R_{40}$ ,  $R_{41}$ ,  $R_{42}$ , and  $R_{43}$  are each independently selected from hydrogen or C<sub>1</sub>-C<sub>8</sub> alkyl.

$R_{16}$  is selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>8</sub> alkylthio C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, and halo.

$R_{13}$  is selected from hydrogen and C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>8</sub> alkyl), C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> phenyl, halophenyl, hydroxyalkyl, and halo, and  $t$  is an integer from 0 to 5.

Preferred specific compounds (and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof) which are illustrative of the compounds of the invention are as follow:

$N$ -[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

$N$ -[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;



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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]glycine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-alanine;

5        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-alanine;

10       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-leucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-leucine;

15       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

20       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

5       [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

10       [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

15       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

20       *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

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The salts of the above indole compounds represented by formulae (I) and (II) are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate,

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bitartrate, borate, bromide, camsylate, carbonate,  
chloride, clavulanate, citrate, chloride, edetate,  
edisylate, estolate, esylate, fluoride, fumarate,  
gluceptate, gluconate, glutamate, glycolylarsanilate,  
5 hexylresorcinat, bromide, chloride, hydroxynaphthoate,  
iodide, isothionate, lactate, lactobionate, laurate,  
malate, malseate, mandelate, mesylate, methylbromide,  
methylnitrate, methylsulfate, mucate, napsylate, nitrate,  
oleate, oxalate, palmitate, pantothenate, phosphate,  
10 polygalacturonate, salicylate, stearate, subacetate,  
succinate, tannate, tartrate, tosylate, trifluoroacetate,  
trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or  
15 more chiral centers and may thus exist in optically active  
forms. Likewise, when the compounds contain an alkenyl or  
alkenylene group there exists the possibility of cis- and  
trans- isomeric forms of the compounds. The R- and S-  
isomers and mixtures thereof, including racemic mixtures  
20 as well as mixtures of cis- and trans- isomers, are  
contemplated by this invention. Additional asymmetric  
carbon atoms can be present in a substituent group such as  
an alkyl group. All such isomers as well as the mixtures  
thereof are intended to be included in the invention. If  
25 a particular stereoisomer is desired, it can be prepared  
by methods well known in the art by using stereospecific

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reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods.

5 For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can  
10 be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable  
15 groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative  
20 form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid  
25 derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides

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prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

10

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

15

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

20

a) The 1H-indole-3-glyoxylamide amino derivative compounds of the invention are prepared by room temperature base catalyzed condensation of the amino acid protected at the acid terminus by protecting group

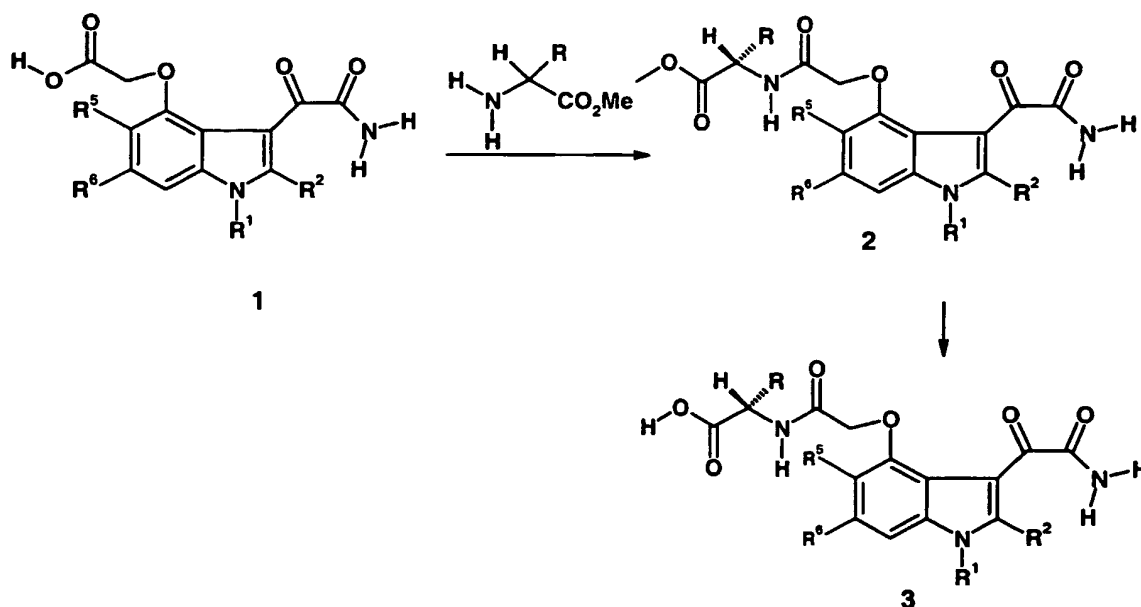
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known in the literature but preferably as the methyl ester with the 1H-indole-3-glyoxylamide acid derivative compound of formula (1) as shown in Scheme I:

5

Scheme 1



Typically, the condensation or coupling is performed in a solvent such as dimethyl formamide, tetrahydrofuran or aqueous mixtures of the like. In general protic solvents are preferred for the purpose of this invention. The reaction is catalyzed by a base including weak organic or inorganic bases. Organic bases such as collidine are preferred. The reaction is also preferably run in the presence of agents that retard or reduce racemization of the amino acid or its

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derivative, such as for example, benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate.

Upon completion of the reaction, the mixture is concentrated in vacuo. The resulting product mixture is  
5 chromatographed to obtain the target compound.

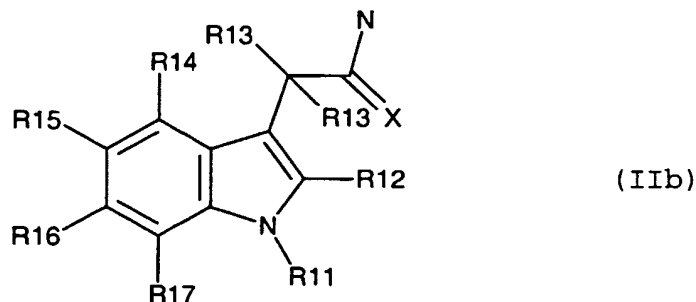
One of skill in the art is aware that the derivatives of the acid such as the acid salt or the methyl ester of the acid, can be reacted with the amino acid or  
10 derivatives thereof to obtain the protected compound 2 or a corresponding derivative. Such methods are well known in the arts and can be found in reference texts such as for example J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C.  
15 Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989. The protected compounds of formula (2) are also useful sPLA<sub>2</sub> inhibitors and are also compounds of this invention.

20       b)     1H-indole-3-acetamide amino acid derivative  
sPLA<sub>2</sub> inhibitors are similarly prepared by condensation of the protected amino acid with the 1H-indole-3-acetamide sPLA<sub>2</sub> inhibitor. The 1H-indole-3-acetamide sPLA<sub>2</sub> inhibitors and methods of making them are set out in U.S.  
25 Patent No. 5,684,034, the entire disclosure of which is incorporated herein by reference. Indole-3-acetamide



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amino acid derivative sPLA2 inhibitors of this invention are represented by compounds of formula (IIb), and pharmaceutically acceptable salts and prodrug derivatives thereof,



5

wherein ;

X is oxygen or sulfur;

R<sub>11</sub> is selected from groups (i), (ii) (iii) and (iv)

10 where;

(i) is C<sub>6</sub>-C<sub>20</sub> alkyl, C<sub>6</sub>-C<sub>20</sub> alkenyl, C<sub>6</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>20</sub> haloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkyl, or

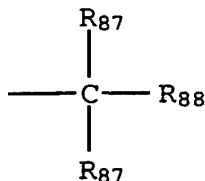
(ii) is aryl or aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkylthio, C<sub>1</sub>-

15 C<sub>10</sub> alkoxy, carboxyl, amino, or hydroxyamino; or

(iii) is -(CH<sub>2</sub>)<sub>n</sub>-(R<sub>80</sub>), or -(NH)-(R<sub>81</sub>), where n is 1 to 8, and R<sub>80</sub> is a group recited in (i), and R<sub>81</sub> is selected from a group recited in (i) or (ii);

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(iv) is



where R<sub>87</sub> is hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl, and R<sub>88</sub> is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C<sub>1</sub>-C<sub>10</sub> alkylthio, C<sub>1</sub>-C<sub>10</sub> alkoxy, phenyl, nitro, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

10 R<sub>12</sub> is halo, C<sub>1</sub>-C<sub>2</sub> alkylthio, C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkyaryl or C<sub>1</sub>-C<sub>2</sub> alkoxy;

each R<sub>13</sub> is independently hydrogen, halo, or methyl;

R<sup>14</sup> is the group -L<sub>C</sub>-[acylamino acid], wherein the acylamino acid group is -C(O)-NR<sup>14a</sup>R<sup>14b</sup> wherein R<sup>14a</sup> is selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl; and -L<sub>C</sub>- is as defined *supra*, and wherein NR<sup>14b</sup> is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. Most preferred are compounds of formula II wherein the group R<sup>14a</sup> is a hydrogen atom (H). A preferred source of the amino acid residue NR<sup>14b</sup> is an amino acid selected from the group comprising isoleucine, valine, phenylalanine,

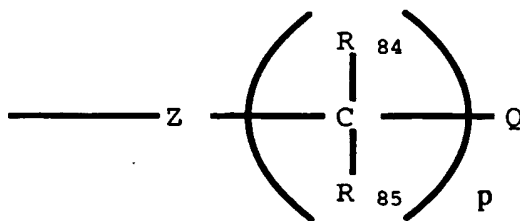
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aspartic acid, leucine, glycine and isomers and derivatives thereof;

$R_{15}$  is selected from hydrogen, a non-interfering substituent, or the group,  $-(L_a)-(acidic\ group)$ ; wherein  
 5  $-(L_a)-$ , is an acid linker having an acid linker length of 1 to 8;

$R_{16}$  and  $R_{17}$  are each independently hydrogen,  $C_1-C_{10}$  alkyl,  $C_1-C_{10}$  alkenyl,  $C_1-C_{10}$  alkynyl,  $C_3-C_8$  cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in  
 10 the set  $R_{15}$ ,  $R_{16}$ , and  $R_{17}$ , combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or  $C_1-C_{10}$  haloalkyl,  $C_1-C_{10}$  alkoxy,  $C_1-C_{10}$  haloalkoxy,  $C_4-C_8$  cycloalkoxy, phenoxy, halo, hydroxy, carboxyl,  $-SH$ ,  $-CN$ ,  
 15  $C_1-C_{10}$  alkylthio, arylthio, thioacetal,  $-C(O)O(C_1-C_{10} alkyl)$ , hydrazide, hydrazino, hydrazido,  $-NH_2$ ,  $-NO_2$ ,  $-NR_{82}R_{83}$ , and  $-C(O)NR_{82}R_{83}$ , where,  $R_{82}$  and  $R_{83}$  are independently hydrogen,  $C_1-C_{10}$  alkyl,  $C_1-C_{10}$  hydroxyalkyl, or taken together with N,  $R_{82}$  and  $R_{83}$  form a 5- to 8-  
 20 membered heterocyclic ring; or a group having the formula;



where,

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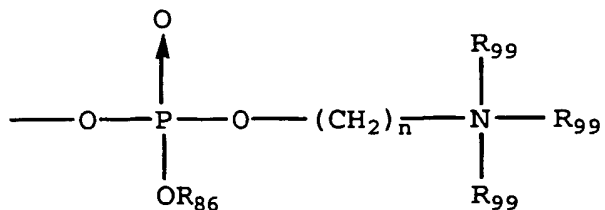
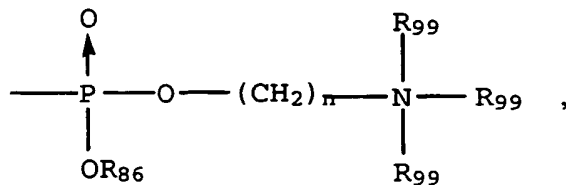
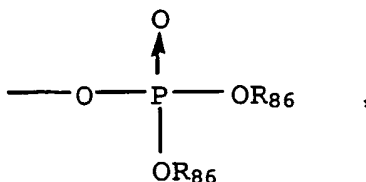
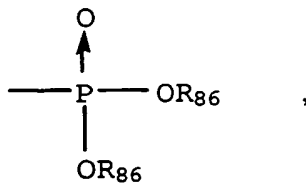
R<sub>84</sub> and R<sub>85</sub> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, hydroxy, or R<sub>84</sub> and R<sub>85</sub> taken together are =O;

p is 1 to 5,

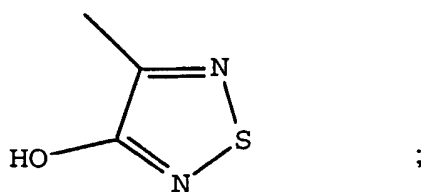
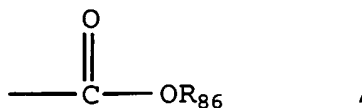
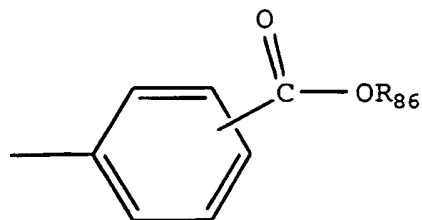
5 Z is a bond, -O-, -N(C<sub>1</sub>-C<sub>10</sub> alkyl)-, -NH-, or -S-;

and

Q is -CON(R<sub>82</sub>R<sub>83</sub>), -5-tetrazolyl, -SO<sub>3</sub>H,

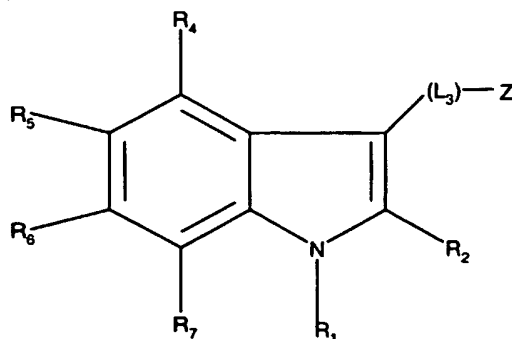


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where n is 1 to 8, R<sub>86</sub> is independently selected from  
 hydrogen, a metal, or C<sub>1</sub>-C<sub>10</sub> alkyl, and R<sub>99</sub> is selected  
 5 from hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl.

c) Indole-3-Oxime amide compounds of the invention  
 are represented by compounds of formula (III) or a  
 pharmaceutically acceptable salt, solvate or prodrug  
 10 thereof;



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wherein ;

$R_1$  is selected from groups (a), (b), and (c)

wherein;

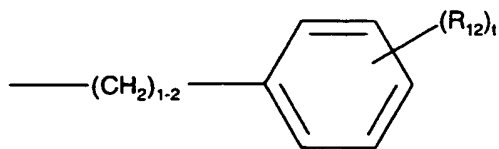
5 (a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or more independently selected non-interfering

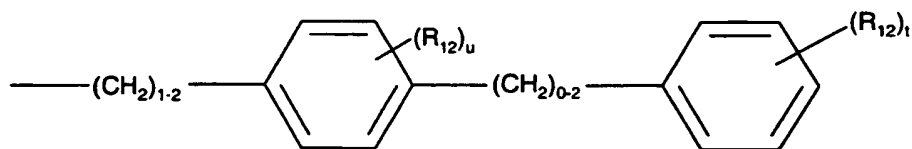
10 substituents; or

(c) is the group  $-(L_1)-R_{11}$ ; where,  $-(L_1)-$  is a divalent linking group of 1 to 8 atoms and where  $R_{11}$  is a group selected from (a) or (b).

15 Particularly preferred are compounds wherein for  $R_1$  the combined group  $-(L_1)-R_{11}$  is selected from the group consisting of



or

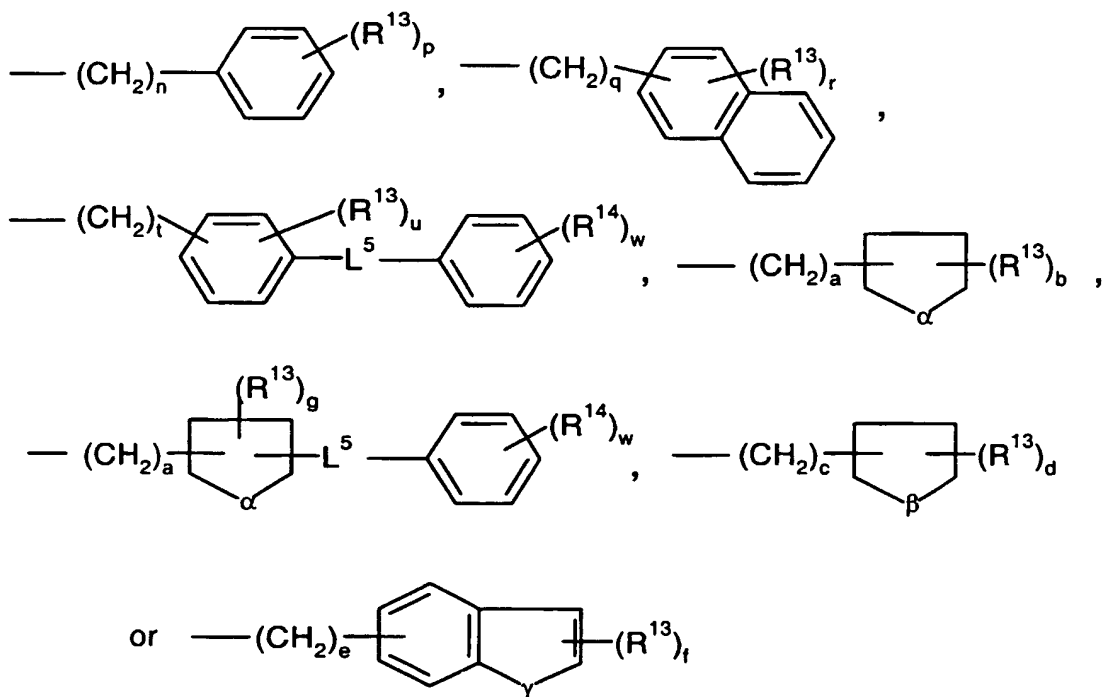


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where  $R_{12}$  is a radical independently selected from halo,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  alkoxy,  $-S-(C_1-C_8 \text{ alkyl})$ ,  $-O-(C_1-C_8 \text{ alkyl})$  and  $C_1$ - $C_8$  haloalkyl where  $t$  is a number from 0 to 5 and  $u$  is a number from 0 to 4.

5

Also preferred for  $R_{11}$  is  $-(CH_2)_m-R^{12}$  wherein  $m$  is an integer from 1 to 6, and  $R^{12}$  is (d) a group represented by the formula:



10

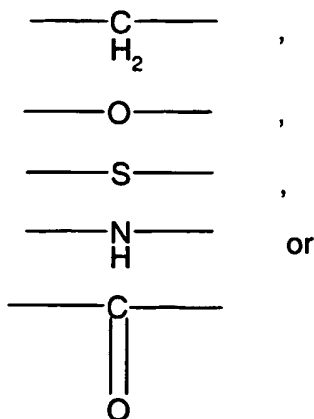
wherein  $a$ ,  $c$ ,  $e$ ,  $n$ ,  $q$ , and  $t$  are independently an integer from 0 to 2,  $R^{13}$  and  $R^{14}$  are independently selected from a halogen,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$  alkyloxy,  $C_1$  to  $C_8$  alkylthio, aryl, heteroaryl, and  $C_1$  to

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$C_8$  haloalkyl,  $\alpha$  is an oxygen atom or a sulfur atom,  $L^5$   
 is a bond,  $-(CH_2)_v-$ ,  
 $-C=C-$ ,  $-CC-$ ,  $-O-$ , or  $-S-$ ,  $v$  is an integer from 0 to 2,  $\beta$   
 is  $-CH_2-$  or  $-(CH_2)_2-$ ,  $\gamma$  is an oxygen atom or a sulfur  
 5 atom,  $b$  is an integer from 0 to 3,  $d$  is an integer from  
 0 to 4,  $f$ ,  $p$ , and  $w$  are independently an integer from 0  
 to 5,  $r$  is an integer from 0 to 7, and  $u$  is an integer  
 from 0 to 4, or is (e) a member of (d) substituted with  
 at least one substituent selected from the group  
 10 consisting of  $C_1$  to  $C_6$  alkyl,  $C_1$  to  $C_8$  alkyloxy,  $C_1$  to  $C_8$   
 haloalkyloxy,  $C_1$  to  $C_8$  haloalkyl, aryl, and a halogen.

$R_2$  is hydrogen, or a group containing 1 to 4 non-  
 hydrogen atoms plus any required hydrogen atoms;

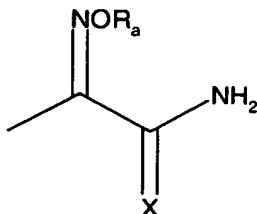
15  $-(L_3)-Z$ , is the group where  $-(L_3)-$  is a divalent  
 linker group selected from a bond or a divalent group  
 selected from:





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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,



5

wherein, X is oxygen or sulfur; and  $R_a$  is selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, aralkyl and -CN;

10  $R_4$  is the group,  $-(L_C)-(acylamino\ acid\ group)$ ; wherein  $-(L_C)-$ , is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

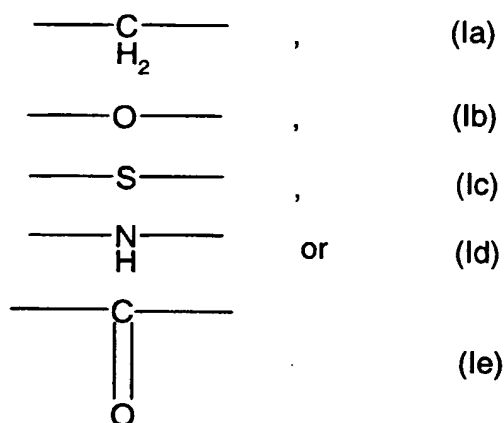
$R_5$  is selected from hydrogen, a non-interfering substituent, or the group,  $-(L_A)-(acidic\ group)$ ; wherein  
15  $-(L_A)-$ , is an acid linker having an acid linker length of 1 to 8.

$R_6$  and  $R_7$  are selected from hydrogen, non-interfering substituent, carbocyclic radical,  
20 carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

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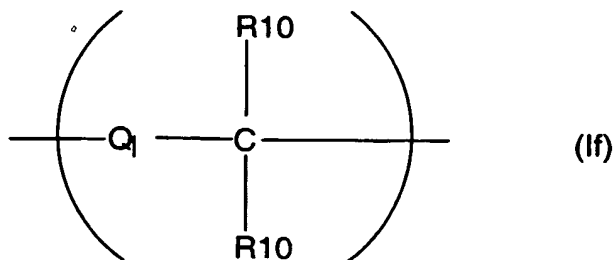
**Preferred Subgroups of Compounds of Formula (III):**  
**Preferred R<sub>1</sub> substituents:**

A preferred subclass of compounds of formula (III)  
 5 are those where for R<sub>1</sub> the divalent linking group -(L<sub>1</sub>)-  
 is a group represented by any one of the following  
 formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



10

or



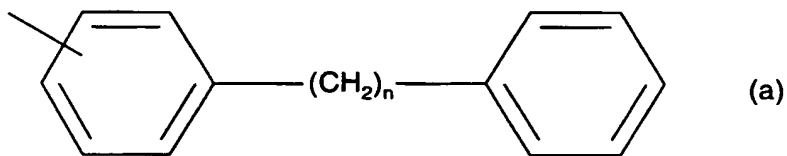
15 where Q<sub>1</sub> is a bond or any of the divalent groups (Ia),  
 (Ib), (Ic), (Id), (Ie), and (If) and each R<sub>10</sub> is

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independently hydrogen, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl or C<sub>1-8</sub> alkoxy.

Particularly preferred as the linking group -(L<sub>1</sub>)- of  
5 R<sub>1</sub> is an alkylene chain of 1 or 2 carbon atoms, namely,  
-(CH<sub>2</sub>)- or -(CH<sub>2</sub>-CH<sub>2</sub>)-.

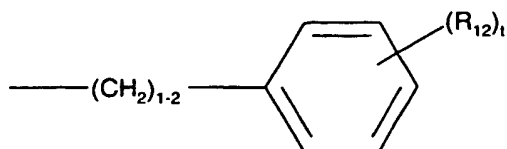
The preferred group for R<sub>11</sub> is a substituted or  
unsubstituted group selected from the group consisting of  
10 C<sub>5</sub>-C<sub>14</sub> cycloalkyl, C<sub>5</sub>-C<sub>14</sub> cycloalkenyl, phenyl, naphthyl,  
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,  
indenyl, stilbenyl, terphenyl, diphenylethylenyl,  
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,  
biphenyl, bibenzyl and related bibenzyl homologues  
15 represented by the formula (a);



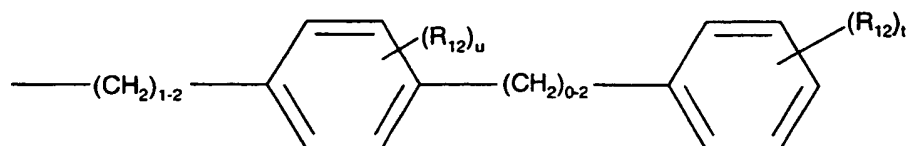
where n is a number from 1 to 8.

20 Particularly preferred are compounds wherein for R<sub>1</sub>  
the combined group -(L<sub>1</sub>)-R<sub>11</sub> is selected from the group  
consisting of

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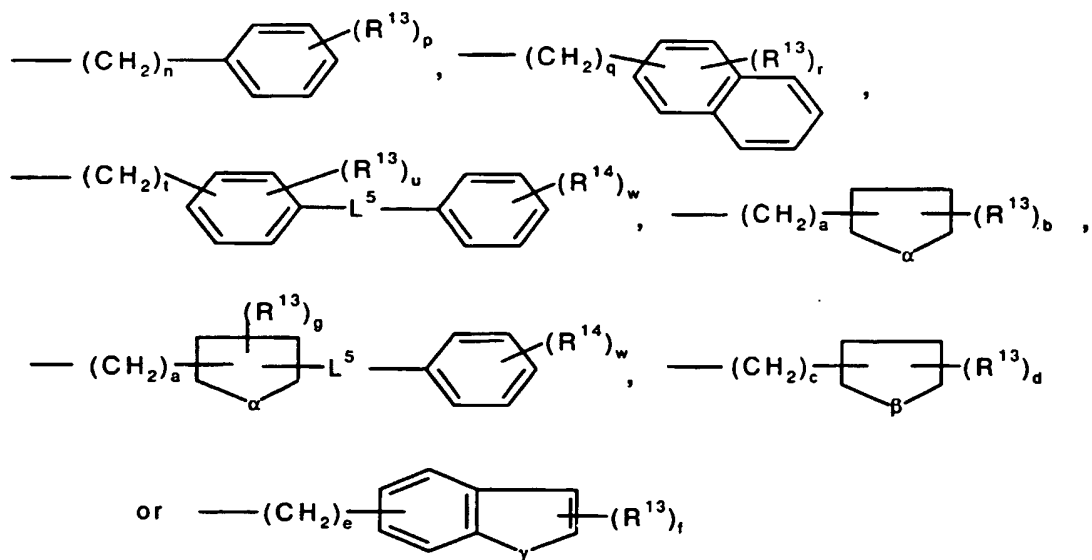


or



where  $R_{12}$  is a radical independently selected from halo,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  alkoxy,  $-S-(C_1-C_8 \text{ alkyl})$ ,  $-O-(C_1-C_8$   
 5  $\text{alkyl})$  and  $C_1$ - $C_8$  haloalkyl where  $t$  is a number from 0 to 5 and  $u$  is a number from 0 to 4.

Also preferred for  $R_{11}$  is  $-(CH_2)_m-R^{12}$  wherein  $m$  is an  
 integer from 1 to 6, and  $R^{12}$  is (d) a group represented by  
 10 the formula:



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wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R<sup>13</sup> and R<sup>14</sup> are independently selected from a halogen, C<sub>1</sub> to C<sub>8</sub> alkyl, C<sub>1</sub> to C<sub>8</sub> alkyloxy, C<sub>1</sub> to C<sub>8</sub> alkylthio, aryl, heteroaryl, and C<sub>1</sub> to C<sub>8</sub> haloalkyl, α is an oxygen atom or a sulfur atom, L<sup>5</sup> is a bond, -(CH<sub>2</sub>)<sub>v</sub>-, -C=C-, -CC-, -O-, or -S-, v is an integer from 0 to 2, β is -CH<sub>2</sub>- or -(CH<sub>2</sub>)<sub>2</sub>-, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C<sub>1</sub> to C<sub>6</sub> alkyl, C<sub>1</sub> to C<sub>8</sub> alkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyl, aryl, and a halogen.

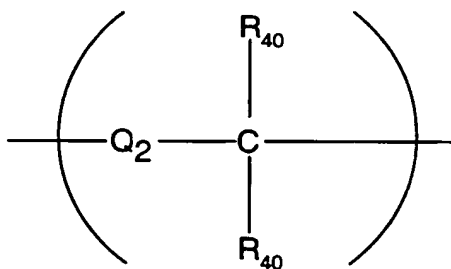
**Preferred R<sub>2</sub> substituents:**

R<sub>2</sub> is preferably selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, -O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -S-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>3</sub>-C<sub>4</sub> cycloalkyl -CF<sub>3</sub>, halo, -NO<sub>2</sub>, -CN, -SO<sub>3</sub>. Particularly preferred R<sub>2</sub> groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF<sub>3</sub>, -Cl, -Br, or -O-CH<sub>3</sub>.

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**Preferred R<sub>4</sub> substituents:**

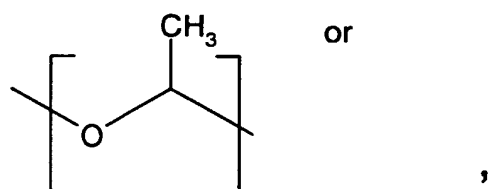
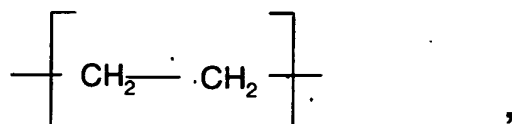
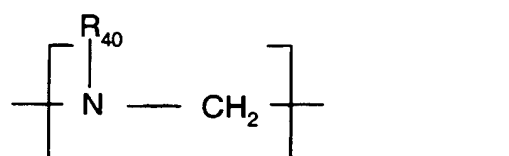
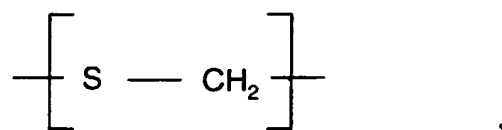
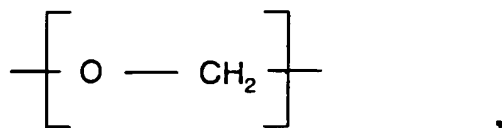
Another preferred subclass of compounds of formula (III) are those wherein R<sub>4</sub> is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, -(L<sub>C</sub>)-, for R<sub>4</sub> is selected from a group represented by the formula;



10

where Q<sub>2</sub> is selected from the group -(CH<sub>2</sub>)-, -O-, -NH-, -C(O)-, and -S-, and each R<sub>40</sub> is independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, -(L<sub>C</sub>)-, for R<sub>4</sub> is selected from the specific groups;

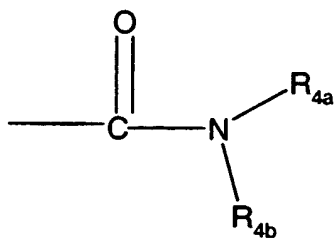
-55-



where  $\text{R}_{40}$  is hydrogen or  $\text{C}_1$  -  $\text{C}_8$  alkyl.

Preferred as the (acylamino acid group) in the group  $\text{R}_4$

5 is the group:



-56-

wherein  $R^{4a}$  is selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl; and wherein  $NR^{4b}$  is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part  
5 of the amino group of the amino acid. A preferred  $R^{4a}$  group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and  
10 derivatives thereof.

A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

15 Particularly preferred are  $R^{4b}$  groups that combine with the nitrogen atom to represent amino acid groups selected from: glycine, glycine methyl ester, L-alanine, L-alanine methylester, L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl  
20 ester, L-phenyl alanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L-valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.

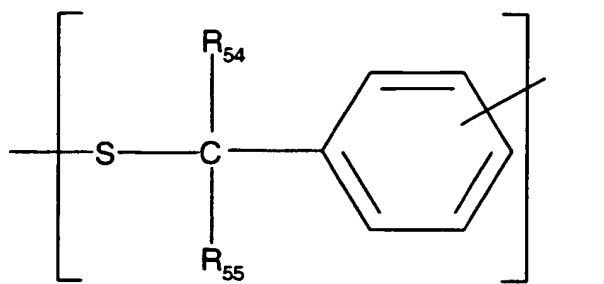
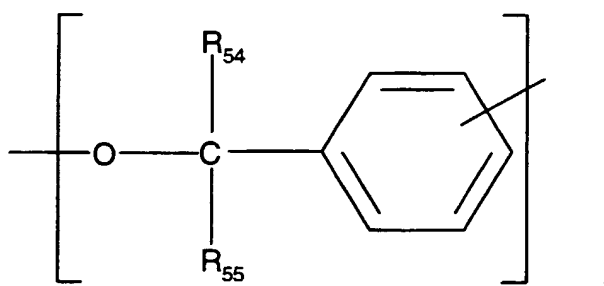


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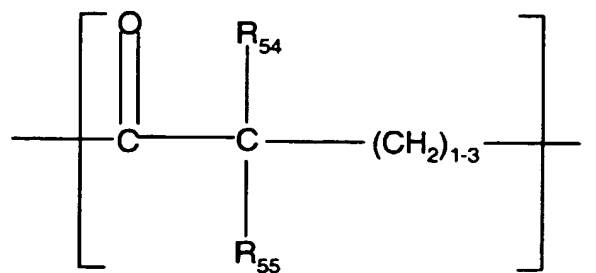
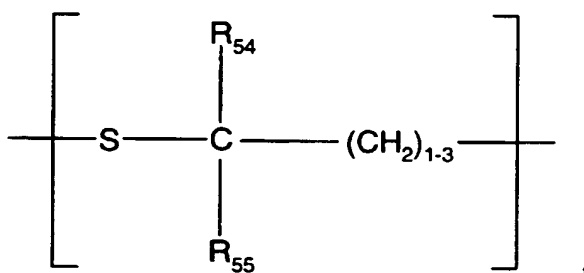
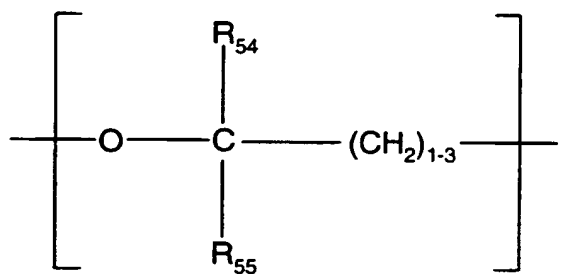
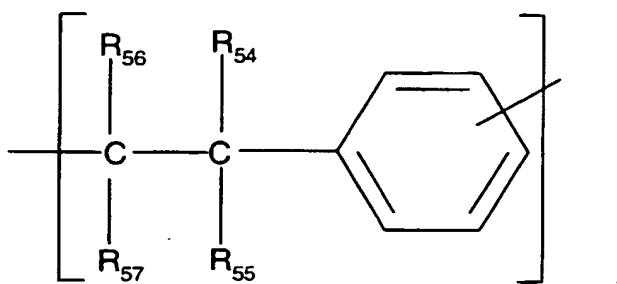
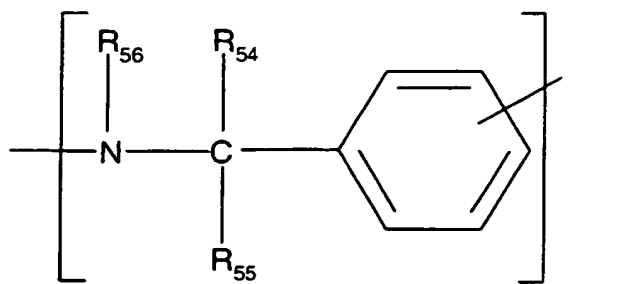
**Preferred R<sub>5</sub> Substituents:**

Preferred acid linker, -(L<sub>a</sub>)-, for R<sub>5</sub> is selected from the group consisting of;

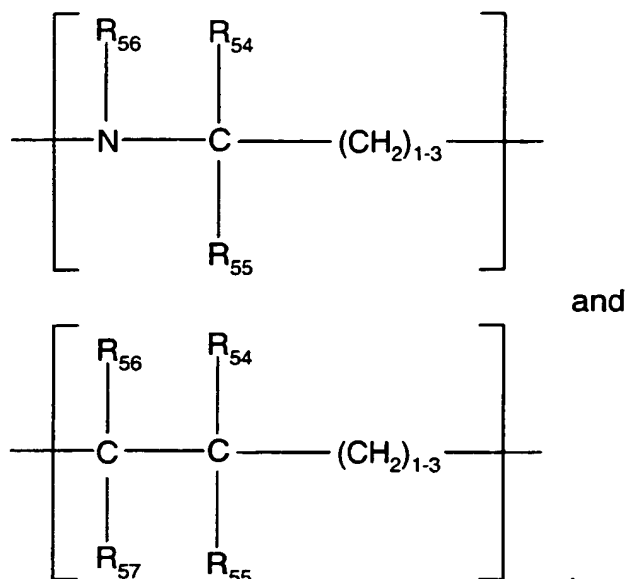
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-59-



wherein R<sub>54</sub>, R<sub>55</sub>, R<sub>56</sub> and R<sub>57</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, or halo. Preferred (acidic group) for R<sub>5</sub> is selected from the group consisting of -CO<sub>2</sub>H, -SO<sub>3</sub>H and -P(O)(OH)<sub>2</sub>

**Preferred R<sub>6</sub> and R<sub>7</sub> substituents:**

Another preferred subclass of compounds of formula (III) are those wherein for R<sub>6</sub> and R<sub>7</sub> the non-interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C<sub>4</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>7</sub>-C<sub>12</sub> aralkyl, C<sub>7</sub>-C<sub>12</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkenyloxy, C<sub>2</sub>-C<sub>6</sub> alkynyloxy, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub>

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alkoxyalkyloxy, C<sub>2</sub>-C<sub>12</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>12</sub>  
alkylcarbonylamino, C<sub>2</sub>-C<sub>12</sub> alkoxyamino, C<sub>2</sub>-C<sub>12</sub>  
alkoxyaminocarbonyl, C<sub>1</sub>-C<sub>12</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> alkylthio,  
C<sub>2</sub>-C<sub>12</sub> alkylthiocarbonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>  
5 alkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub>  
haloalkylsulfonyl, C<sub>2</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl,  
-C(O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl), benzyloxy,  
phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino,  
bromo, carbamyl, carboxyl, carbalkoxy, -(CH<sub>2</sub>)<sub>n</sub>-CO<sub>2</sub>H,  
10 chloro, cyano, cyanoguanidiny, fluoro, guanidino,  
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,  
iodo, nitro, phosphono, -SO<sub>3</sub>H, thioacetal, thiocarbonyl,  
and carbonyl; where n is from 1 to 8.

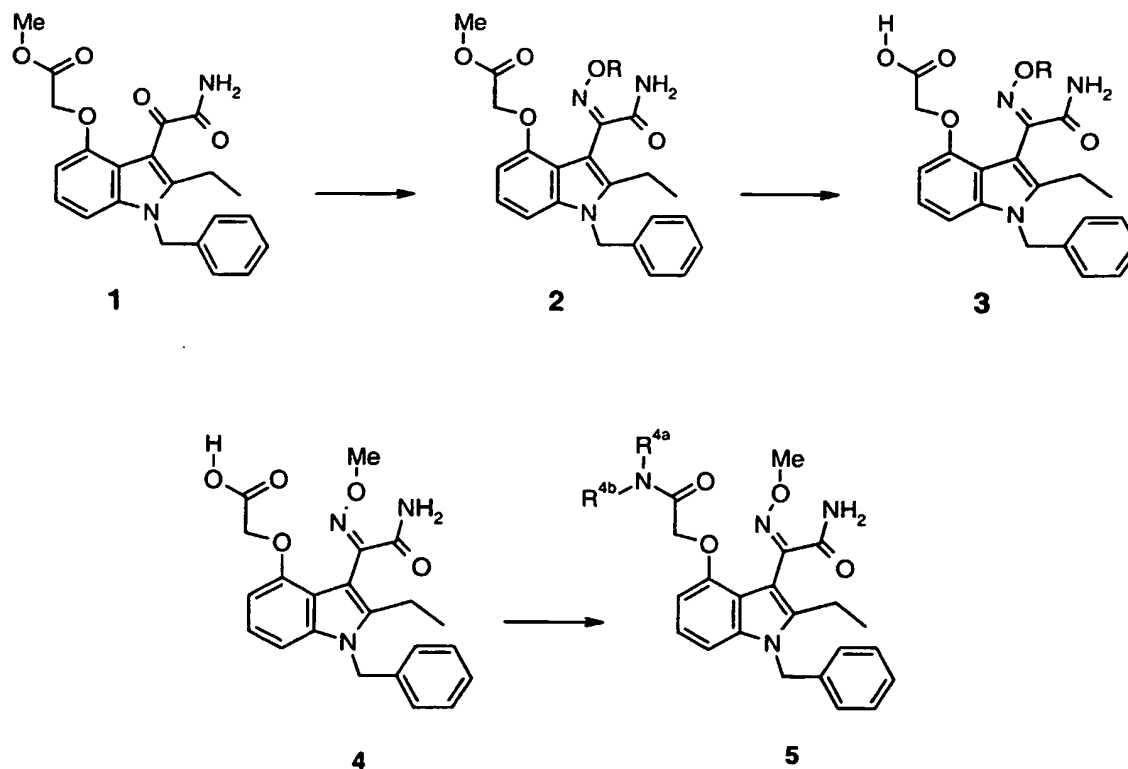
15 Most preferred as non-interfering substituents are  
methyl, ethyl, propyl, and isopropyl.

The indole-3-oxime compounds of the invention can be  
prepared following protocol of scheme 2 below;

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Scheme 2



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To introduce the oxime functionality, the methyl ester of the glyoxylamide (compound 10 in scheme 1, compound 1 in scheme 2, *supra*.) is heated with hydroxylamine hydrochloride (when R is H) in a THF/methanol mixture for 8 hours or until the reaction was deemed complete. The reaction product is isolated by chromatography or other known laboratory procedure to afford a white solid. Substituted oximes such as when R is methyl, ethyl, phenyl or other substituent can be prepared by reacting the corresponding substituted hydroxylamine hydrochloride or free base with the

15

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glyoxylamide as described *supra*. The ester functionality at the 4 or 5 position on the indole nucleus, as in for example, compound 2, can be: (a) converted to the acid by hydrolysis using lithium hydroxide or other known ester hydrolysis methods to afford compounds of formula 3, or (b) converted to an amide functionality directly or via the acid functionality to afford compounds of formula 4. General procedures for the conversion of organic acids to amino acid are well known to artisans in the field, and have been documented in general reference texts including, for example, J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989.

15

The oxime acid compounds of formula 3 such as the methyloxime compound such as that of formula 4 can be converted to the corresponding amino acid derivative via the methylester by coupling with various amino acids by general coupling procedures known to one skilled in the art. Additional references, or procedures are found in J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985; R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989 and J. Jones Amino Acids and Peptide

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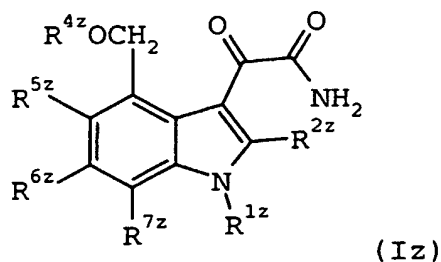
Synthesis, Oxford Science Publications, Stephen G. Davis, Editor, Oxford University Press Inc., New York, NY, 1992.

5    **III. Method of Making the 1H-Indole-3-Glyoxylamide Starting Material for Preparing the Compounds of the Invention:**

          The synthesis of the indole compounds of the  
10    invention (viz., Compounds of Formulae I and II) can be accomplished by well known methods as recorded in the chemical literature. In particular, the indole starting materials may be prepared by the synthesis schemes taught in US Patent No. 5,654,326; the disclosure of  
15    which is incorporated herein by reference. Another method of making 1H-indole-3-glyoxylamide sPLA<sub>2</sub> inhibitors is described in United States Patent Application Serial No. 09/105381, filed June 26, 1998 and titled, "Process for Preparing 4-substituted 1-H-  
20    Indole-3-glyoxyamides" the entire disclosure of which is incorporated herein by reference.

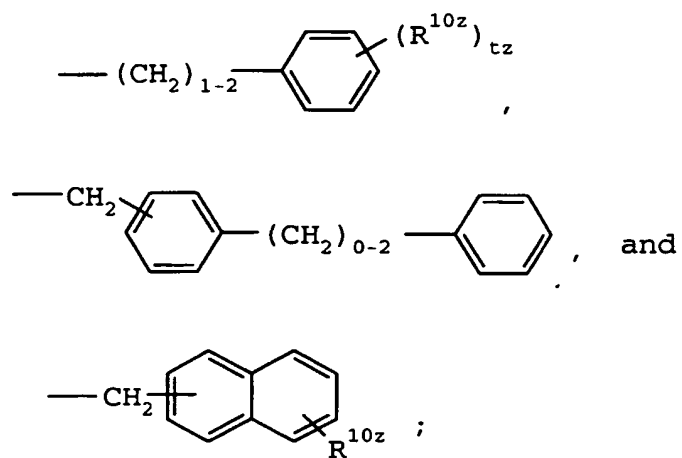
          United States Patent Application Serial  
No. 09/105381 discloses the following process having  
25    steps (a) thru (i):  
          Preparing a compound of the formula (Iz) or a pharmaceutically acceptable salt or prodrug derivative thereof

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5 wherein:

$R^{1z}$  is selected from the group consisting of  $-C_7-C_{20}$  alkyl,



where

10  $R^{10z}$  is selected from the group consisting of halo,  $C_1-C_{10}$  alkyl,  $C_1-C_{10}$  alkoxy,  $-S-(C_1-C_{10}$  alkyl) and halo( $C_1-C_{10}$ )alkyl, and  $tz$  is an integer from 0 to 5 both inclusive;

$R^{2z}$  is selected from the group consisting of  
 15 hydrogen, halo,  $C_1-C_3$  alkyl,  $C_3-C_4$  cycloalkyl,  $C_3-C_4$



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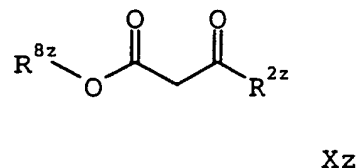
cycloalkenyl, -O-(C<sub>1</sub>-C<sub>2</sub> alkyl), -S-(C<sub>1</sub>-C<sub>2</sub> alkyl), aryl, aryloxy and HET;

R<sup>4z</sup> is the group -CO<sub>2</sub>H, or salt and prodrug derivative thereof; and

5 R<sup>5z</sup>, R<sup>6z</sup> and R<sup>7z</sup> are each independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo(C<sub>2</sub>-C<sub>6</sub>)alkyl, bromo, chloro, fluoro, iodo and aryl;

which process comprises the steps of:

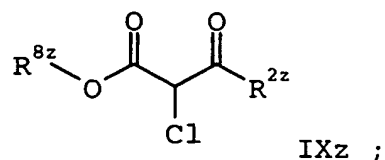
10 a) halogenating a compound of formula Xz



where R<sup>8z</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl or HET;

with SO<sub>2</sub>Cl<sub>2</sub> to form a compound of formula

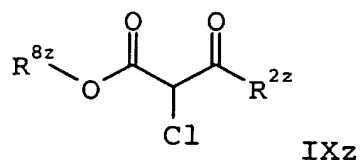
15 IX



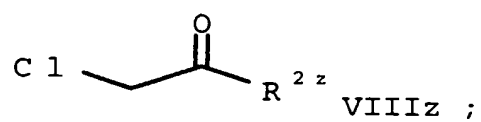
b) hydrolyzing and decarboxylating a compound of formula IXz

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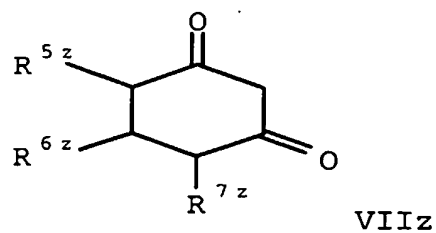
-66-



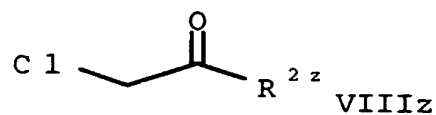
to form a compound of formula VIIIz



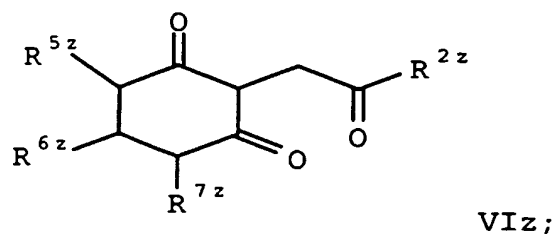
c) alkylating a compound of formula VIIz



with a compound of formula VIIIz

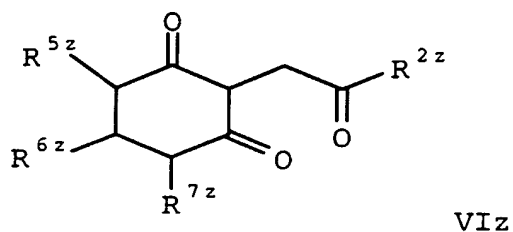


to form a compound of formula VIz



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- d) aminating and dehydrating a compound of formula VIz

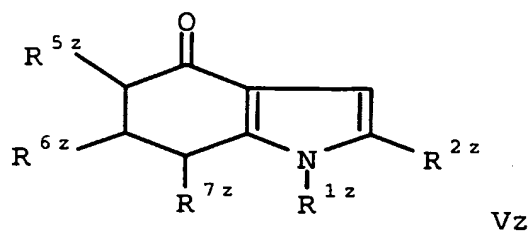


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with an amine of the formula  $R^{1z}NH_2$  in the presence of a solvent that forms an azeotrope with water to form a compound of formula Vz;

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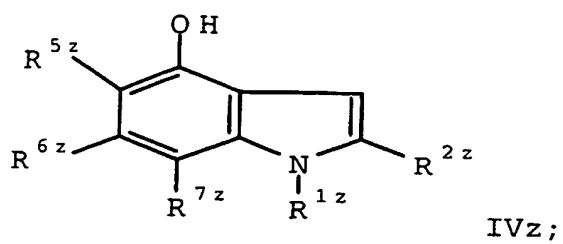
- e) oxidizing a compound of formula Vz



by refluxing in a polar hydrocarbon solvent having a boiling point of at least 150 °C and a dielectric constant of at least 10 in the presence of a catalyst to form a compound of formula IVz

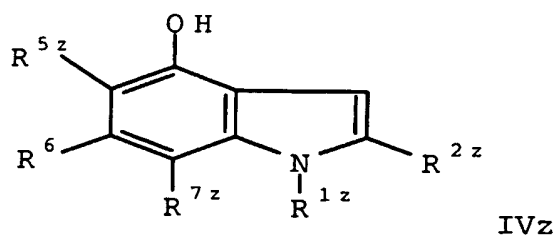
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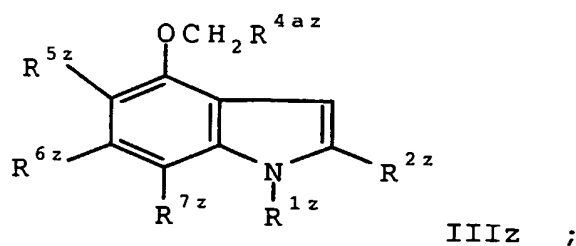


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f) alkylating a compound of the formula IVz

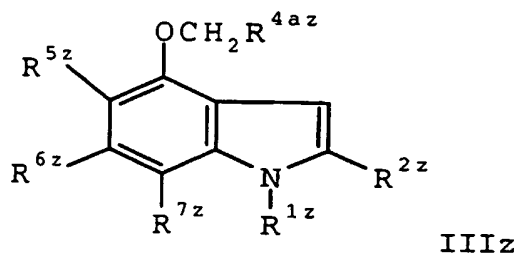


5 with an alkylating agent of the formula  $XCH_2R^{4az}$  where X is a leaving group and  $R^{4az}$  is  $-CO_2R^{4b}$ , where  $R^{4bz}$  is an acid protecting group to form a compound of formula IIIz



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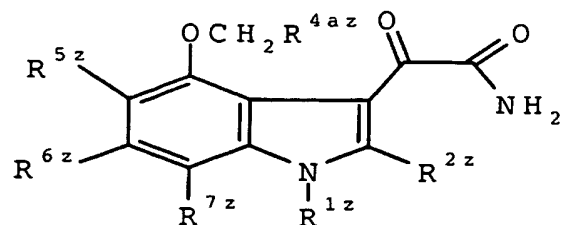
g) reacting a compound of formula IIIz



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with oxalyl chloride and ammonia to form a compound of formula IIz

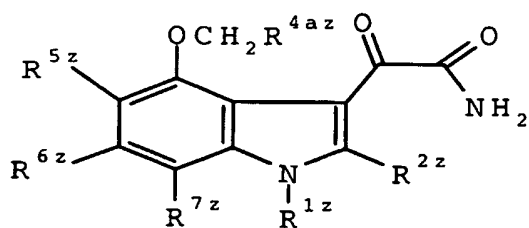
-70-



IIz; and

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h) optionally hydrolyzing a compound of  
formula IIz



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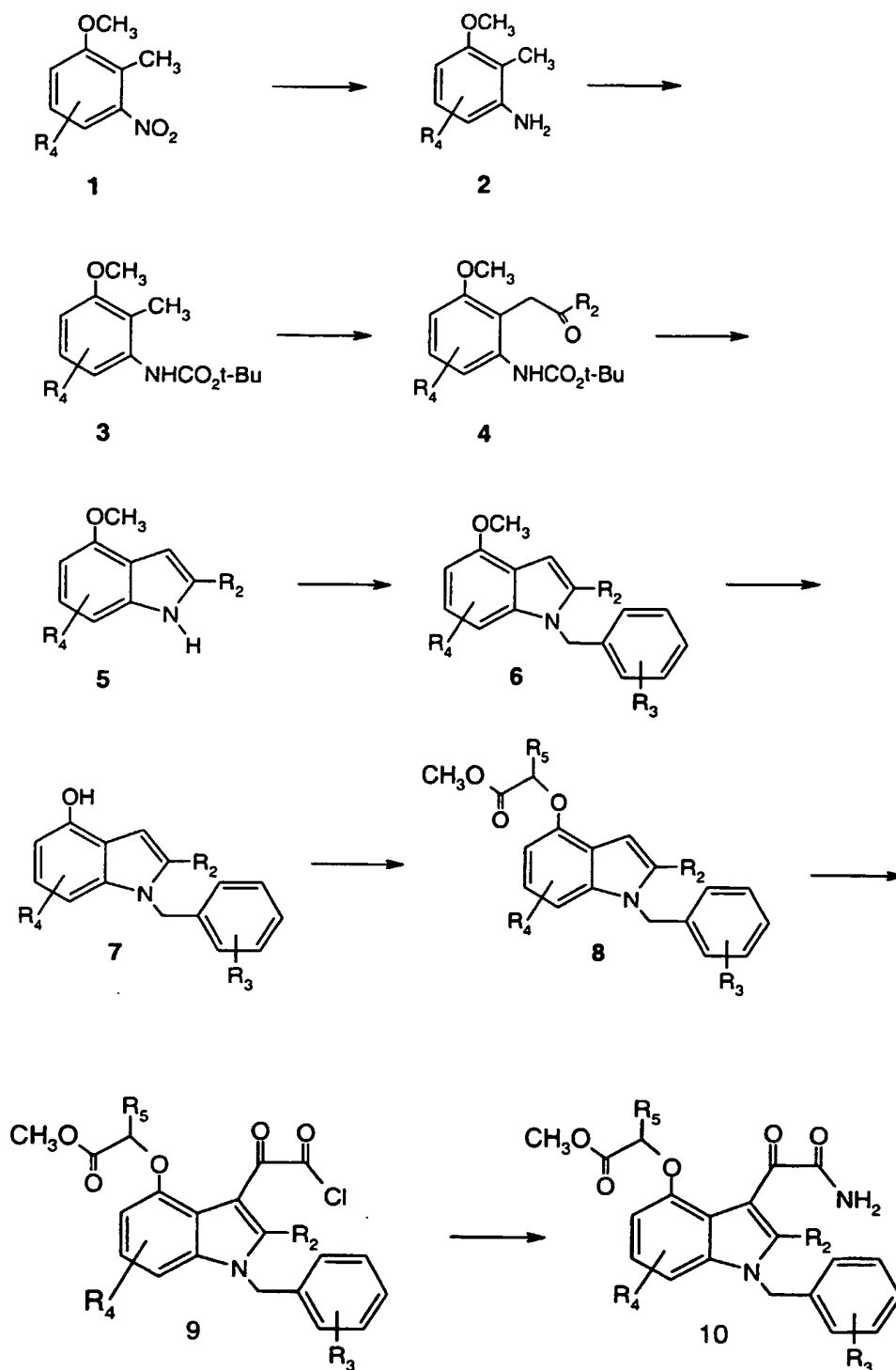
IIz

to form a compound of formula Iz.

An alternative protocol useful for the synthesis of  
the starting material is shown in Scheme 1 below:

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## Scheme 1



5 The synthesis of indole-3-oxime amides (compound of formula I and II, supra.) of this invention uses

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as starting material the glyoxamide ((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)acetic acid methyl ester, compound 10, *supra*. This starting material is prepared as set out in the preceding section or by the method of Example 9 of U.S. Patent No. 5,654,326 (the disclosure of which is incorporated herein by reference).

To obtain the glyoxylamide starting material substituted in the 4-position with an (acidic group) linked through an oxygen atom, the reactions outlined in the scheme *supra*, are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, *Synthesis*, 1991, 871-878, the disclosures of which are incorporated herein by reference). The starting material ortho-nitrotoluene, 1, is readily reduced to 2-methyl,3-methoxyaniline, 2. Reduction of 1 is by the catalytic hydrogenation of the corresponding nitrotoluene using palladium on carbon as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline 2, obtained, is converted to the N-tert-butylloxycarbonyl derivative 3, in good yield, on heating with di-tert-butyl dicarbonate in THF at reflux temperature. The dilithium salt of the dianion of 3 is



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generated at -40 to -20°C in THF using sec-butyllithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide to form the ketone 4. This product (4) may be purified by crystallization from hexane, or reacted  
5 directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25°C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated with  
10 an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100°C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-demethylated by stirring with boron tribromide in methylene chloride for  
15 approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, *Adv. Drug Res.*, 1977, 12, 176, the disclosure of which is incorporated herein by reference). The 4-hydroxyindole, 7, is alkylated with an alpha bromoalkanoic acid ester in dimethylformamide (DMF) using  
20 sodiumhydride as a base, with reaction condition of 5 to 6. The  $\alpha$ -[(indol-4-yl)oxy]alkanoic acid ester, 8, is reacted with oxalyl chloride in methylene chloride to give 9, which is not purified but reacted directly with ammonia to give the glyoxamide 10.

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Glyoxamide starting material compounds substituted at the 5 position of the indole nucleus with an (acidic group) may be prepared by methods and starting materials shown in schemes 2 and 3 of Patent No. 5,654,326; the disclosure of which is incorporated herein by reference.

#### **IV. Methods of Using the Compounds of the Invention:**

The indole compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) sPLA<sub>2</sub>, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting sPLA<sub>2</sub> mediated release of fatty acids comprises contacting mammalian sPLA<sub>2</sub> with an therapeutically effective amount of indole compounds corresponding to Formulae (I) or (II) as described herein including salt or a prodrug derivative thereof.

Another aspect of this invention is a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress

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syndrome, pancreatitis, trauma, bronchial asthma,  
allergic rhinitis, rheumatoid arthritis, osteoarthritis,  
and related diseases which comprises administering to a  
mammal (including a human) a therapeutically effective  
5 dose of the indole compound of the invention (see,  
formulae I and II).

As previously noted the compounds of this invention  
are useful for inhibiting sPLA<sub>2</sub> mediated release of  
10 fatty acids such as arachidonic acid. By the term,  
"inhibiting" is meant the prevention or therapeutically  
significant reduction in release of sPLA<sub>2</sub> initiated  
fatty acids by the compounds of the invention. By  
"pharmaceutically acceptable" it is meant the carrier,  
15 diluent or excipient must be compatible with the other  
ingredients of the formulation and not deleterious to  
the recipient thereof.

The specific dose of a compound administered  
20 according to this invention to obtain therapeutic or  
prophylactic effects will, of course, be determined by the  
particular circumstances surrounding the case, including,  
for example, the compound administered, the route of  
administration and the condition being treated. Typical  
25 daily doses will contain a non-toxic dosage level of from

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about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention (per Formula I  
5 or II) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of  
10 composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The  
15 dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and  
20 intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the indole compound of the invention  
25 together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical

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formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound.

The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also

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act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

5           Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or  
10   acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

          In powders the carrier is a finely divided solid which is in admixture with the finely divided Active  
15   ingredient. In tablets the Active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active  
20   ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa  
25   butter.

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Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended  
5 in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely  
10 divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 thru 8 are illustrative only and are not intended to limit the  
15 scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or (II) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

#### Formulation 1

20 Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

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**Formulation 2**

A tablet is prepared using the ingredients below:

	<u>Quantity</u> <u>(mg/tablet)</u>
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

5

The components are blended and compressed to form tablets each weighing 665 mg

**Formulation 3**

10        An aerosol solution is prepared containing the following components:

	<u>Weight</u>
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

15        The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and



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diluted with the remainder of the propellant. The valve units are then fitted to the container.

#### Formulation 4

5        Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

10        The Active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and

15        passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each

20        weighing 150 mg.

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**Formulation 5**

Capsules, each containing 80 mg of Active ingredient,  
are made as follows:

5

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

The Active ingredient, cellulose, starch, and  
magnesium stearate are blended, passed through a No. 45  
mesh U.S. sieve, and filled into hard gelatin capsules in  
10 200 mg quantities.

**Formulation 6**

Suppositories, each containing 225 mg of Active  
ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

15

The Active ingredient is passed through a No. 60 mesh  
U.S. sieve and suspended in the saturated fatty acid  
glycerides previously melted using the minimum heat  
necessary. The mixture is then poured into a suppository  
20 mold of nominal 2 g capacity and allowed to cool.

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**Formulation 7**

Suspensions, each containing 50 mg of Active ingredient per 5 ml dose, are made as follows:

5

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

10

**Formulation 8**

An intravenous formulation may be prepared as follows:

15

Active ingredient	100 mg
Isotonic saline	1,000 ml

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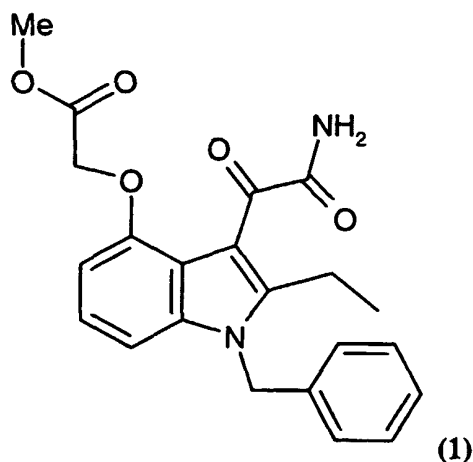
The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

5 All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory nmr and IR spectra. They also had the correct mass spectral values.

10

**Example 1**

Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, a compound represented by the compound of formula (1) formula:



15

**Part A. Preparation of 2-Ethyl-4-methoxy-1H-indole.**

A solution of 140 mL (0.18 mol) of 1.3M sec-butyl lithium in cyclohexane was added slowly to N-tert-  
20 butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol)

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in 250 mL of THF keeping the temperature below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to 0°C and then the bath replaced. After the temperature had cooled to -60°C,  
5 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of ether and 400 mL of 0.5N HCl.  
10 The organic layer was separated, washed with water, brine, dried over  $\text{MgSO}_4$ , and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(tert-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of  
15 trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was chromatographed three  
20 times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for  $\text{C}_{11}\text{H}_{13}\text{NO}$ :

Calculated: C, 75.40; H, 7.48; N, 7.99

Found: C, 74.41; H, 7.64; N, 7.97.

25

**Part B. Preparation of 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.**

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2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/mineral oil was added. After 1.5 hours, 2.9 mL (24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

**Part C. Preparation of 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole.**

3.1g (11.7 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole was O-demethylated by treating it with 48.6 mL of 1M  $\text{BBr}_3$  in methylene chloride with stirring at room temperature for 5 hours, followed by concentration at reduced pressure. The residue was dissolved in ethyl acetate, washed with brine and dried ( $\text{MgSO}_4$ ). After concentrating at reduced pressure, the residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to give 1.58g (54% yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole, mp, 86-90°C.

Analyses for  $\text{C}_{17}\text{H}_{17}\text{NO}$ :

Calculated: C, 81.24; H, 6.82; N, 5.57  
Found: C, 81.08; H, 6.92; N, 5.41.

**Part D. Preparation of [[2-Ethyl-1-(phenylmethyl)-**

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**1H-indol-4-yl]oxy]acetic acid methyl ester.**

2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole (1.56g, 6.2 mmol) was added to a mixture of 248mg (6.2 mmol) of 60% NaH/mineral oil in 20mL DMF and stirred for 0.67 hour.

5

Then 0.6 mL(6.2 mmol) of methyl bromoacetate was added and stirring was continued for 17 hours. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc/hexane, to give 1.37g (69% yield) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, 89-92°C.

15 Analyses for  $\text{C}_{20}\text{H}_{21}\text{NO}_3$ :

Calculated: C, 74.28; H, 6.55; N, 4.33

Found: C, 74.03; H, 6.49; N, 4.60.

20 **Part E. Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.**

Oxalyl chloride (0.4 mL, 4.2 mmol) was added to 1.36g (4.2 mmol) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester in 10 mL of methylene chloride and the mixture stirred for 1.5 hours. The mixture was concentrated at reduced pressure and residue taken up in 10 mL of methylene chloride. Anhydrous ammonia was bubbled in for 0.25 hours, the mixture stirred

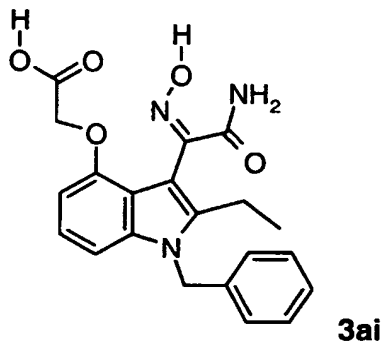
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for 1.5 hours and evaporated at reduced pressure. The residue was stirred with 20 mL of ethyl acetate and the mixture filtered. The filtrate was concentrated to give 1.37g of a mixture of [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and ammonium chloride. This mixture melted at 172-187°C.

**Example 2**

10 (indol-3-oxime amide starting material)

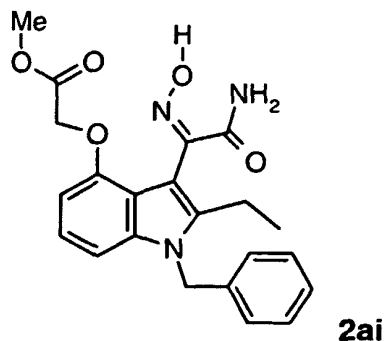
2-[[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.



A. Preparation of 2-[[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.



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A stirred mixture of **1** (600 mg, 1.52 mmol) and hydroxylamine hydrochloride (528 mg, 7.60 mmol) in THF (4 mL)/CH<sub>3</sub>OH (4 mL) was heated at 55 °C for 8 h. After  
5 concentration at ambient temperature, the residue was chromatographed on silica (gradient 0-40% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound **2ai** (285 mg) as a white solid in 46% yield. IR (CHCl<sub>3</sub>) 3510, 3415, 1757, 1667 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  1.17 (t, *J* = 7.5 Hz, 3H), 2.84  
10 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.73 (s, 2H), 5.36 (s, 2H), 5.67 (br s, 1H), 6.31 (br s, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.98-7.07 (m, 3H), 7.23-7.32 (m, 3H); ESIMS *m/e* 410 (*M*<sup>+</sup>+1).

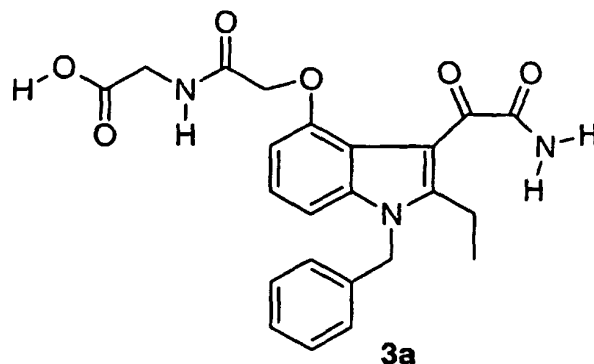
Elemental Analyses for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>·0.30(H<sub>2</sub>O):

15        Calculated: C, 63.70; H, 5.73; N, 10.13;  
         Found:        C, 63.68; H, 5.62; N, 10.20.

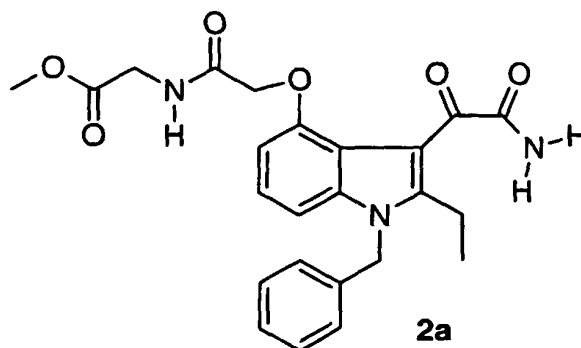
### Example 3

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
20 indol-4-yl]oxy]acetyl]glycine

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**A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester**



5

To a solution of **1** (0.100 g, 0.249 mmol) in 2 mL DMF was added collidine (0.069 mL, 0.523 mmol), methyl glycine hydrochloride (0.0313 g, 0.249 mmol), and benzotriazolyl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.115 g, 0.261) sequentially at room temperature. After 2.5 hrs. the reaction mixture was concentrated *in vacuo* to near dryness, then it was taken up in CH<sub>2</sub>Cl<sub>2</sub>, chromatographed on a silica gel column (gradient 20-40% THF in CH<sub>2</sub>Cl<sub>2</sub>) and dried in an 80°C vacuum oven to give 0.0768 g of **2a** as a yellow solid in 68% yield. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.04 (t, *J* = 6.8 Hz, 3H), 2.90 (br q, *J* = 6.8 Hz, 2H),

10

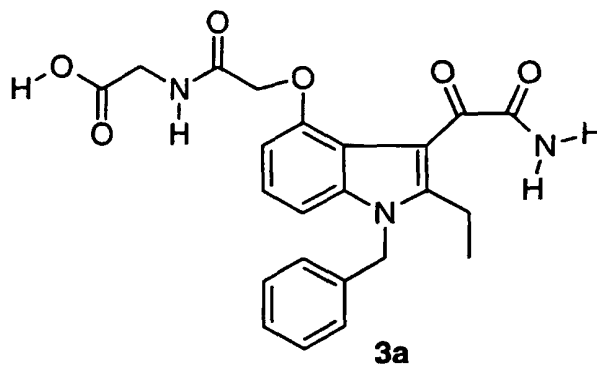
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3.57 (s, 3H), 3.88 (d,  $J = 5.5$  Hz, 2H), 4.57 (s, 2H), 5.51 (s, 2H), 6.59 (d,  $J = 5.6$  Hz, 1H), 7.01-7.08 (m 4H), 7.19-7.30 (m, 3H), 7.55 (s, 1H), 7.99 (s, 1H), 8.40 (t,  $J = 5.5$  Hz, 1H).

5

**B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine**



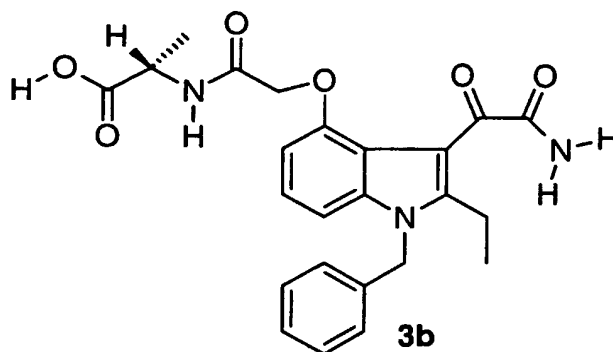
10 To a solution of 2a (0.035 g, 0.078 mmol) in 1 mL THF, 1 mL MeOH and 0.25 mL distilled H<sub>2</sub>O was added 4.17N LiOH (0.093 mL, 0.388 mmol) at room temperature. After 2 hrs. the reaction mixture was acidified with 5N HCl (0.093 mL, 0.465 mmol) and concentrated *in vacuo*. The residue  
15 was taken up in CH<sub>2</sub>Cl<sub>2</sub>, then rapidly triturated with hexanes to give a yellow suspension which was filtered and dried in an 80°C vacuum oven to give 0.0336 g of 3a as a yellow solid in 99% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.04 (t,  $J = 5.9$  Hz, 3H), 2.90 (br q,  $J = 5.9$  Hz, 2H), 3.80 (d,  $J = 4.8$  Hz, 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d,  $J = 5.8$  Hz, 1H),  
20 2H), 7.01-7.08 (m 4H), 7.19-7.30 (m, 3H), 7.55 (s, 1H), 7.99 (s, 1H), 8.40 (t,  $J = 5.5$  Hz, 1H).

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7.01-7.28 (m, 7H), 7.54 (s, 1H), 7.99 (s, 1H), 8.31 (t,  $J$  = 4.8 Hz, 1H), 12.25-12.75 (br s, 1H).

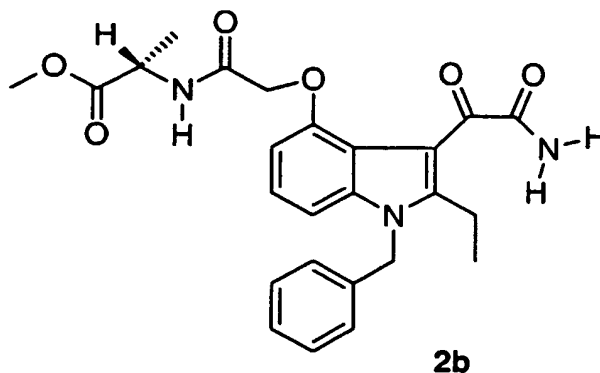
**Example 4**

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine



A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester

10



Following the experimental procedure as described for 2a, 2b was obtained as a yellow solid in 65% yield.

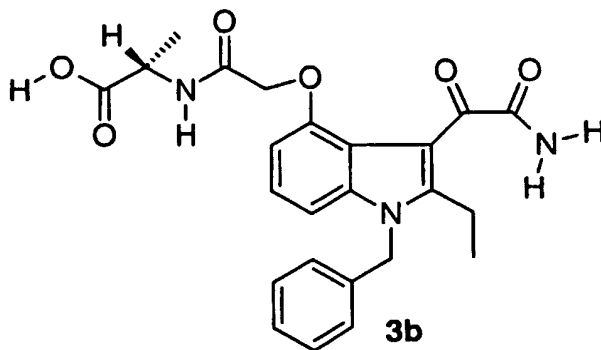
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t,  $J$  = 7.2 Hz, 3H), 1.29 (d,  $J$  = 7.3 Hz, 3H), 2.91 (br q,  $J$  = 7.2 Hz, 2H), 3.54 (s, 3H), 4.29 (qd,  $J$  = 7.3, 6.8 Hz, 1H), 4.55 (s, 2H), 5.51 (s,

15

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2H), 6.57 (m, 1H), 6.99 (d,  $J = 7.4$  Hz, 2H), 7.07-7.08 (m, 2H), 7.21-7.31 (m, 3H), 7.56 (s, 1H), 8.05 (s, 1H), 8.40 (d,  $J = 6.8$  Hz, 1H).

5      **B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine**

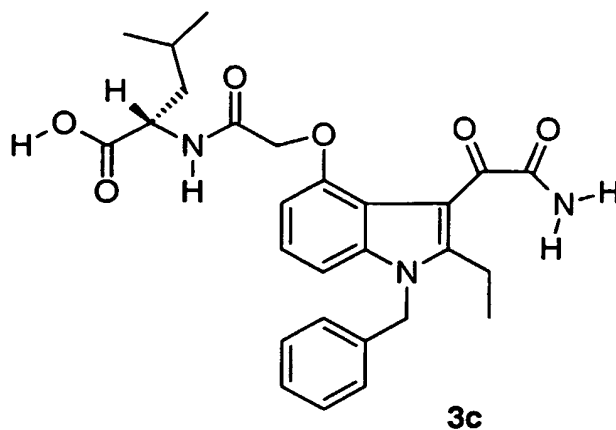


Following the experimental procedure as described for  
 10 preparing compound 3a, compound 3b, was obtained as a  
 yellow solid in 89% yield.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.04 (t,  $J$   
 = 7.2 Hz, 3H), 1.29 (d,  $J = 7.3$  Hz, 3H), 2.91 (br q,  $J$   
 = 7.2 Hz, 2H), 4.22 (td,  $J = 7.2, 7.1$  Hz, 1H), 4.54 (s, 2H),  
 5.51 (s, 2H), 6.60 (d,  $J = 6.3$  Hz, 1H), 7.00-7.09 (m, 4H),  
 15 7.21-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.31 (d,  $J$   
 = 7.1 Hz, 1H), 12.75-12.84 (br s, 1H).

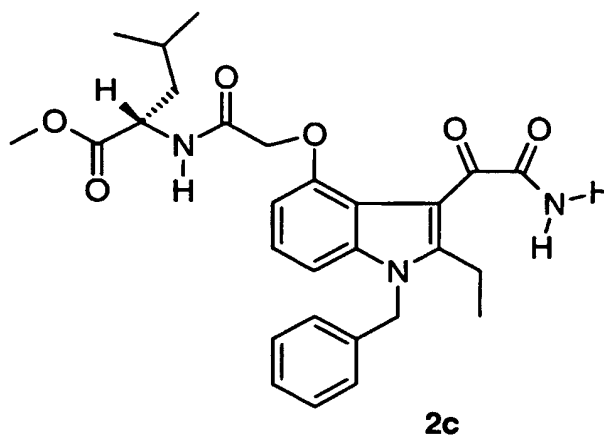
**Example 5**

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
 20 indol-4-yl]oxy]acetyl]-L-leucine

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A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester



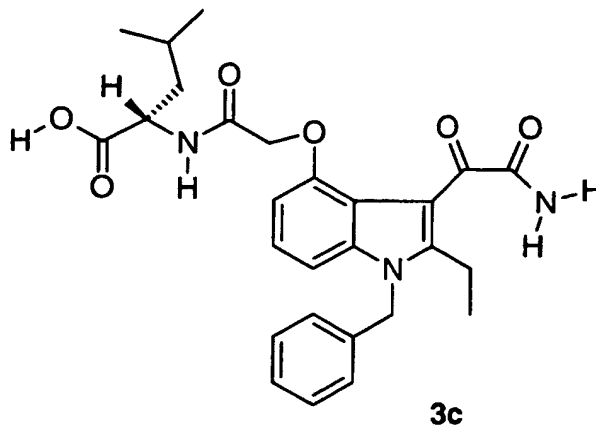
5

Following the experimental procedure as described for 2a, 2c was obtained as a yellow solid in 98% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.67 (d, *J* = 5.5 Hz, 3H), 0.72 (d, *J* = 5.7 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.30-1.50 (m, 2H), 1.51-1.64 (m, 1H), 2.91 (br q, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 4.20-4.27 (m, 1H), 4.57 (s, 2H), 5.52 (s, 2H), 6.53-6.56 (m, 1H), 6.97-7.08 (m, 4H), 7.21-7.29 (m, 3H), 7.56 (s, 1H), 8.07 (s, 1H), 8.37 (d, *J* = 7.3 Hz, 1H).

10

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**B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine**



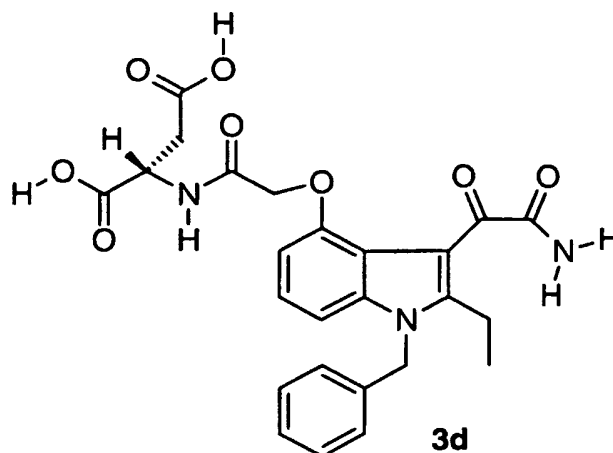
5 Following the experimental procedure as described for 3a, 3c was obtained as a yellow solid in 75% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.76 (d, J = 5.7 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.39-1.43 (m, 1H), 1.69 (t, J = 7.3 Hz, 2H), 2.96 (br q, J = 7.3 Hz, 2H), 4.57-4.65  
10 (m, 1H), 4.69 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 5.38 (s, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.95-7.12 (m, 5H), 7.26-7.32 (m, 3H), 8.17 (d, J = 8.2 Hz, 1H).

15

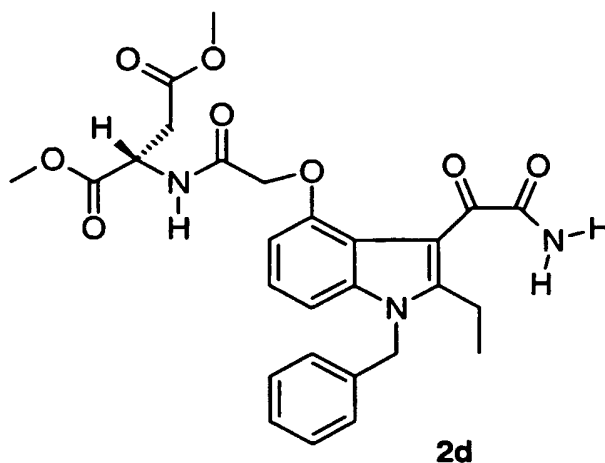
**Example 6**

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid

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**A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester**



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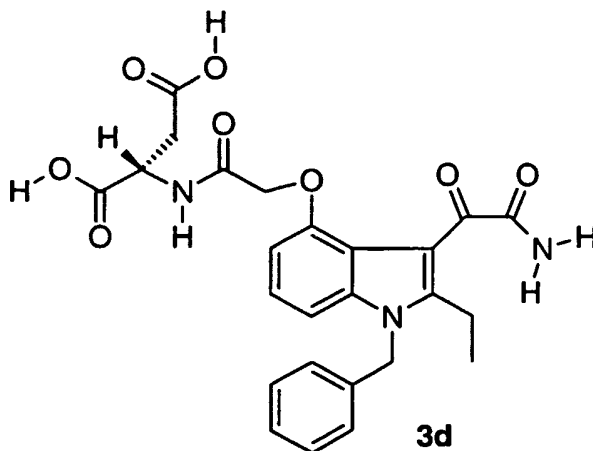
Following the experimental procedure as described for 2a, 2d was obtained as a yellow solid in 88% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t, J = 7.3 Hz, 3H), 2.72 (dd, J = 16.6, 7.1 Hz, 1H), 2.83 (dd, J = 16.7, 7.1 Hz, 1H), 2.90 (br q, J = 7.3 Hz, 2H), 3.49 (s, 3H), 3.55 (s, 3H), 4.54 (s, 2H), 4.66 (m, 1H), 5.51 (s, 2H), 6.54 (m, 1H), 6.97-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.50 (s, 1H), 7.97 (s, 1H), 8.52 (d, J = 7.9 Hz, 1H).

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**B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid**



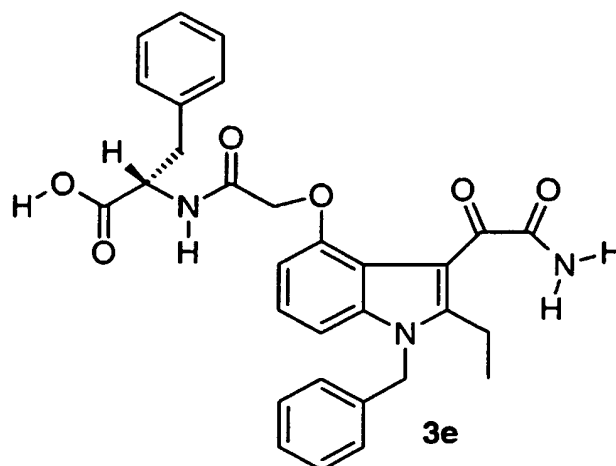
5

Following the experimental procedure as described for 3a, 3d was obtained as a yellow solid in 99% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t, *J* = 7.2 Hz, 3H), 2.52-2.76 (m, 2H), 2.90 (br q, *J* = 7.2 Hz, 2H), 4.53 (s, 2H), 4.53-4.60 (m, 1H), 5.50 (s, 2H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.19-7.30 (m, 3H), 7.47 (s, 1H), 7.94 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 12.40-13.20 (br s, 2H).

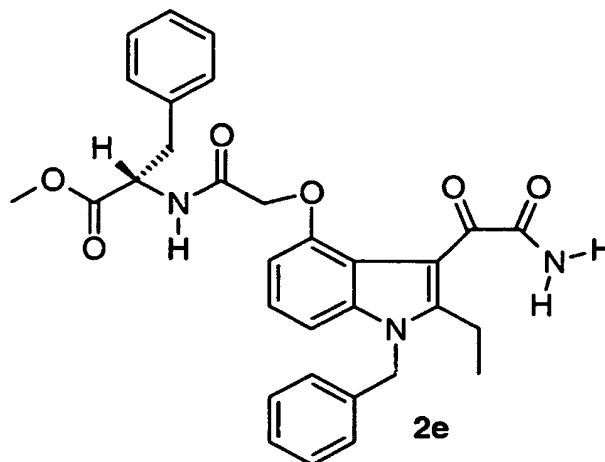
**Example 7**

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine**

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**A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-phenylalanine methyl ester**

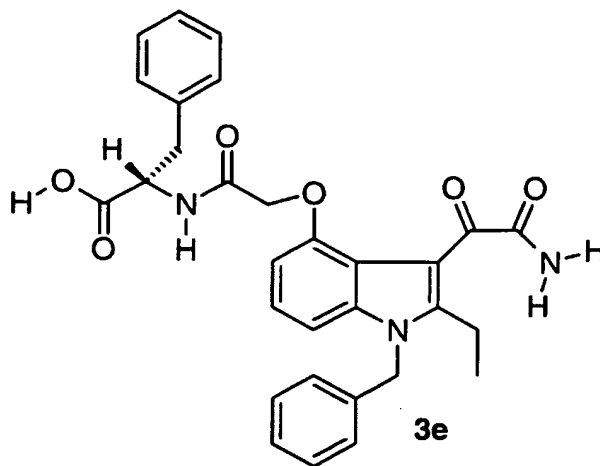


5

Following the experimental procedure as described for 2a, 2e was obtained as a yellow solid in 68% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.06 (t, *J* = 7.2 Hz, 3H), 2.88-3.03 (m, 4H), 3.54 (s, 3H), 4.47-4.50 (m, 1H), 4.50 (s, 2H), 5.52 (s, 2H), 6.41 (d, *J* = 7.7 Hz, 1H), 6.98-7.11 (m, 9H), 7.21-7.30 (m, 3H), 7.47 (s, 1H), 8.06 (s, 1H), 8.52 (d, *J* = 7.7 Hz, 1H).

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**B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine**



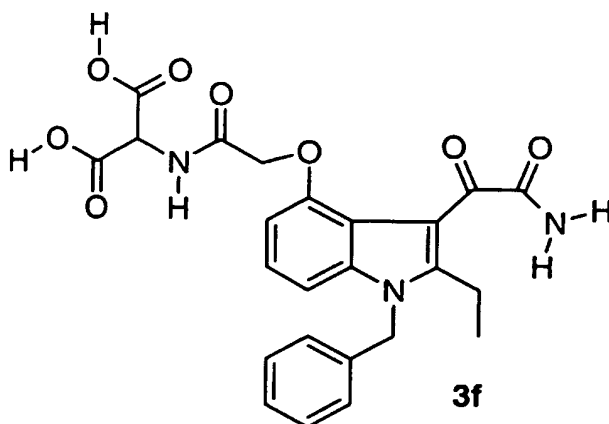
5

Following the experimental procedure as described for 3a, 3e was obtained as a yellow solid in 93% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.04 (t, J = 7.1 Hz, 3H), 2.85-3.12 (m, 4H), 4.17-4.26 (m, 1H), 4.54 (s, 2H), 5.51 (s, 2H), 6.59 (d, J = 6.4 Hz, 1H), 6.98-7.09 (m, 9H), 7.19-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.30 (d, J = 7.0 Hz, 1H), 12.50 (br s, 1H).

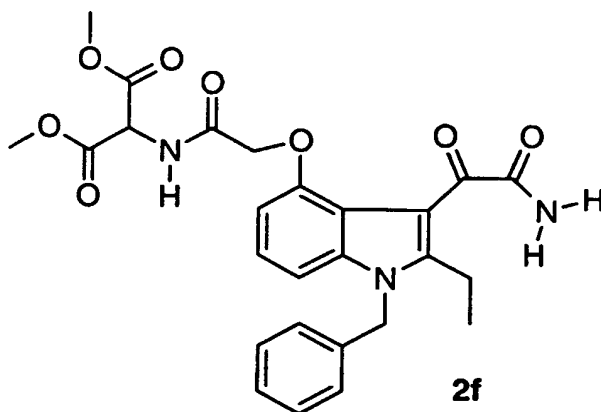
**Example 8**

15 **[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid**

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**A. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester**



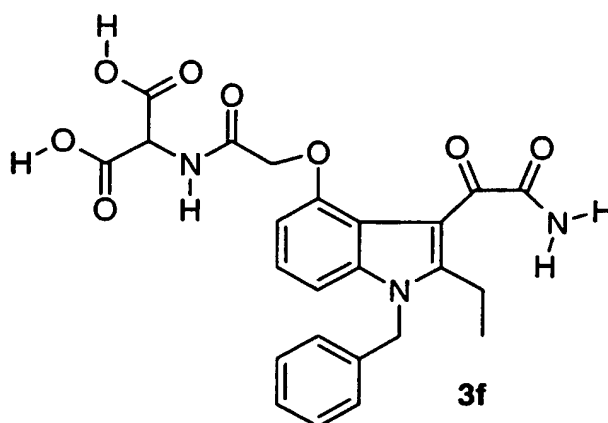
5

Following the experimental procedure as described for 2a, 2f was obtained as a yellow solid in 98% yield.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.04 (t,  $J$  = 7.3 Hz, 3H), 2.90 (br q,  $J$  = 7.3 Hz, 2H), 3.64 (s, 6H), 4.63 (s, 2H), 5.16 (d,  $J$  = 7.1 Hz, 1H), 5.51 (s, 2H), 6.54-6.56 (m, 1H), 6.98-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.43 (s, 1H), 7.88 (s, 1H), 8.90 (d,  $J$  = 7.2 Hz, 1H).

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**B. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid**

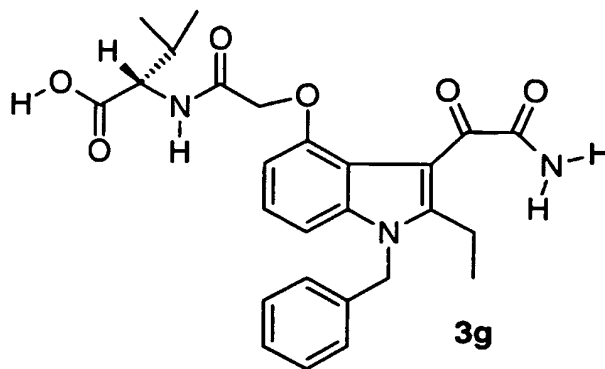


Following the experimental procedure as described for 3a,  
5 3f was obtained as a yellow solid in 99% yield. <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 1.04 (t, J = 6.9 Hz, 3H), 2.89 (br q, J = 7.3  
Hz, 2H), 4.62 (s, 2H), 4.91 (d, J = 7.2 Hz, 1H), 5.50 (s,  
2H), 6.57 (d, J = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.18-  
7.30 (m, 3H), 7.37 (s, 1H), 7.83 (s, 1H), 8.55 (d, J = 7.2  
10 Hz, 1H), 12.30-13.00 (br s, 2H).

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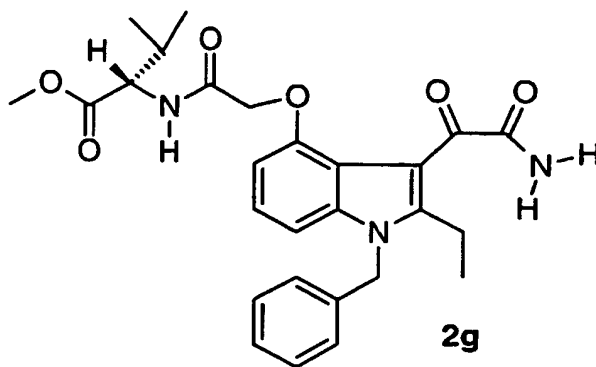
## Example 9

**N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine**



5

**A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester**



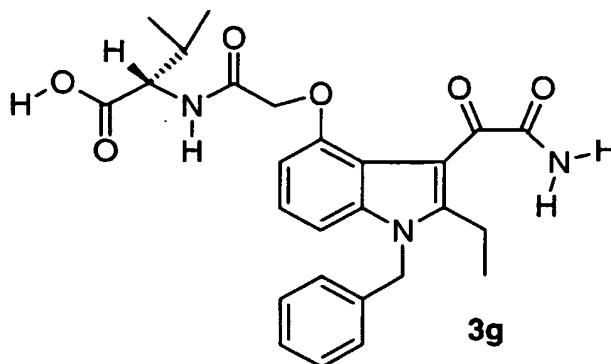
10 Following the experimental procedure as described for 2a, 2g was obtained as a yellow solid in 96% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.71 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.99-2.05 (m, 1H), 2.90 (br q, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 4.11 (br t, *J* = 7.0 Hz, 1H), 4.60 (s, 2H), 5.52 (s, 2H), 6.52 (d, *J* = 4.4 Hz, 1H),

15

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6.95 (d,  $J = 7.2$  Hz, 2H), 7.06 (br s, 2H), 7.18-7.29 (m, 3H), 7.52 (s, 1H), 8.04 (s, 1H), 8.20 (d,  $J = 7.8$  Hz, 1H).

**B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine**

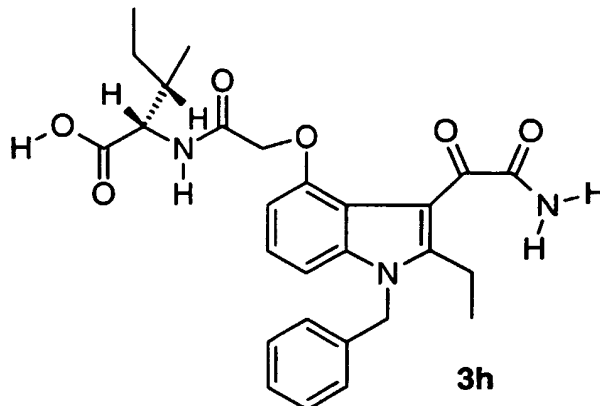


Following the experimental procedure as described for 3a, 3g was obtained as a yellow solid in 94% yield.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  0.71 (d,  $J = 6.9$  Hz, 3H), 0.75 (d,  $J = 6.8$  Hz, 3H), 1.04 (t,  $J = 7.3$  Hz, 3H), 2.01-2.07 (m, 1H), 2.90 (br q,  $J = 7.3$  Hz, 2H), 4.09 (br dd,  $J = 7.9, 6.2$  Hz, 1H), 4.60 (s, 2H), 5.51 (s, 2H), 6.54 (d,  $J = 6.1$  Hz, 1H), 6.95 (d,  $J = 7.3$  Hz, 2H), 6.99-7.08 (m, 2H), 7.18-7.29 (m, 3H), 7.49 (s, 1H), 8.01 (s, 1H), 8.08 (d,  $J = 8.2$  Hz, 1H), 12.63 (br s, 1H).

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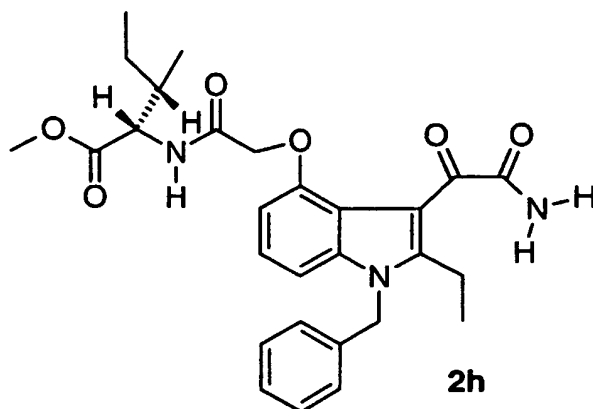
**Example 10**

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-isoleucine**



5

**A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-*L*-isoleucine methyl ester**



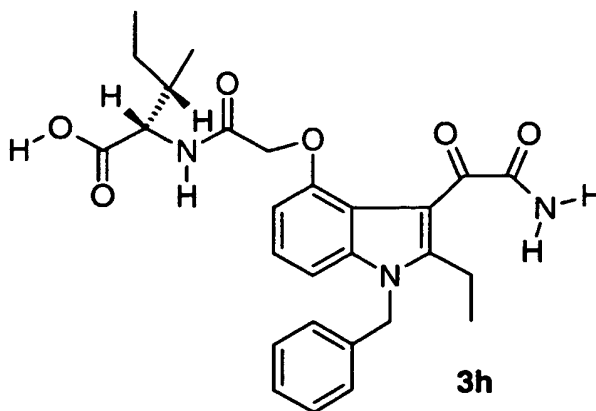
10 Following the experimental procedure as described for 2a, 2h was obtained as a yellow solid in 73% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.64-0.71 (m, 6H), 0.99-1.08 (m, 4H), 1.21-1.26 (m, 1H), 1.76-1.80 (m, 1H), 2.91 (br q, *J* = 7.4 Hz, 2H), 3.53 (s, 3H), 4.15 (br t, *J* = 7.2 Hz, 1H), 4.60 (s,



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2H), 5.52 (s, 2H), 6.52 (m, 1H), 6.96 (d,  $J = 7.2$  Hz, 2H), 7.02-7.07 (m, 2H), 7.18-7.29 (m, 3H), 7.53 (s, 1H), 8.04 (s, 1H), 8.23 (d,  $J = 7.7$  Hz, 1H).

5            **B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-L-isoleucine**



Following the experimental procedure as described for 3a,  
10 3h was obtained as a yellow solid in 92% yield.  $^1\text{H}$  NMR  
(DMSO- $d_6$ )  $\delta$  0.64-0.84 (m, 6H), 1.04 (t,  $J = 7.2$  Hz, 3H),  
1.21-1.28 (m, 2H), 1.76-1.80 (m, 1H), 2.91 (br q,  $J = 7.2$   
Hz, 2H), 4.12 (br t,  $J = 7.3$  Hz, 1H), 4.59 (s, 2H), 5.51  
(s, 2H), 6.55 (d,  $J = 6.4$  Hz, 1H), 6.96 (d,  $J = 7.2$  Hz,  
15 2H), 7.01-7.08 (m, 2H), 7.21-7.29 (m, 3H), 7.51 (s, 1H),  
8.01 (s, 1H), 8.11 (d,  $J = 7.4$  Hz, 1H), 12.40-12.65 (br s,  
1H).

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**Assay**

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A<sub>2</sub>. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A<sub>2</sub> on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

## 15 Reagents:

## REACTION BUFFER -

CaCl<sub>2</sub>·2H<sub>2</sub>O (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)

20 (Sigma A-7030, product of Sigma  
Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

## ENZYME BUFFER -

25 0.05 NaOAc.3H<sub>2</sub>O, pH 4.5

0.2 NaCl

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Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

5 racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-sn-glycero-3-phosphorylcholine

TRITON X-100<sup>TM</sup> prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

10 A measured volume of racemic dipheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar

TRITON X-100<sup>TM</sup> nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB  
15 to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mM Triton X-100<sup>TM</sup> detergent, and 0.12 mM DTMB in a buffered aqueous solution at pH 7.5.

20

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
- 25 3. Add 50 nanograms of sPLA<sub>2</sub> (10 microliters) to appropriate wells;

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4. Incubate plate at 40 °C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

5 All compounds were tested in triplicate. Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured  
10 at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC<sub>50</sub> values were determined. Typically, the IC<sub>50</sub> values (see, Table I,  
15 below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405  
20 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC<sub>50</sub> values. IC<sub>50</sub> were determined by  
25 plotting log concentration versus inhibition values in the range from 10-90% inhibition.

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Results of Human Secreted Phospholipase A<sub>2</sub> Inhibition  
Tests

Table

Compound No. from Examples 3-10	Inhibition of human secreted PLA <sub>2</sub> IC <sub>50</sub> ± mean deviation (3-4 tests) (nM)
1	49
2A	529
2B	533
2C	82
2D	874
2E	666
2F	698
2G	283
2H	166
3A	71
3B	59
3C	28
3D	132
3E	64
3F	44.7
3G	36.4
3H	25.1

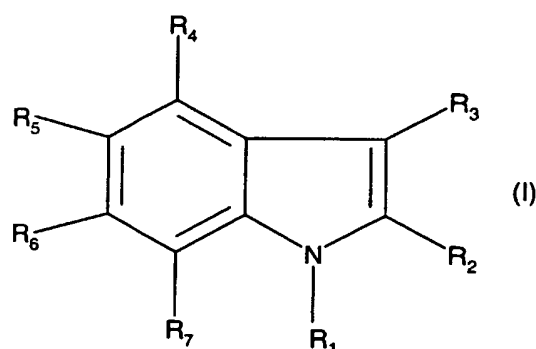
5       The compound of Example 1 is highly active in  
inhibiting sPLA<sub>2</sub>.

While the present invention has been illustrated  
above by certain specific embodiments, it is not intended  
10   that these specific examples should limit the scope of the  
invention as described in the appended claims.

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WE CLAIM:

1. An indole compound represented by the formula  
(I), or a pharmaceutically acceptable salt, solvate, or  
5 prodrug derivative thereof;



wherein ;

- 10  $R_1$  is selected from groups (a), (b), and (c)

wherein;

(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

- 15 (b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

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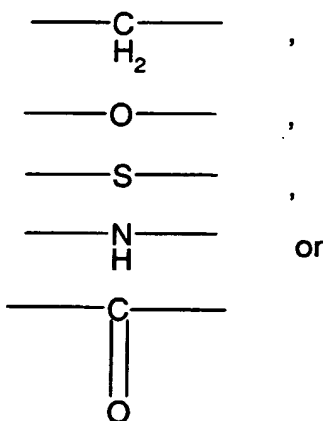
(c) is the group  $-(L_1)-R_{11}$ ; where,  $-(L_1)-$  is a divalent linking group of 1 to 8 atoms and where  $R_{11}$  is a group selected from (a)

or (b);

5  $R_2$  is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

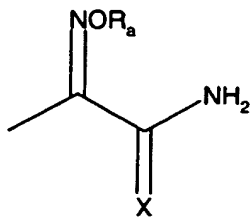
$R_3$  is  $-(L_3)-Z$ , where  $-(L_3)-$  is a divalent linker group selected from a bond or a divalent group selected from:

10

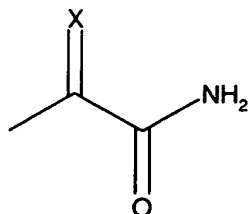


and Z is selected from a group represented by the formulae,

15

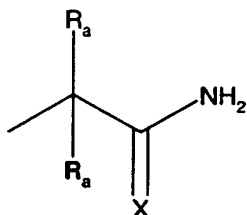


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or

5



wherein, X is oxygen or sulfur; and R<sub>a</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkaryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, aralkyl and -CN;

10 R<sub>4</sub> is the group, -(L<sub>C</sub>)-(acylamino acid group); wherein -(L<sub>C</sub>)-, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R<sub>5</sub> is selected from hydrogen, a non-interfering substituent, or the group, -(L<sub>A</sub>)-(acidic group); wherein  
15 -(L<sub>A</sub>)-, is an acid linker having an acid linker length of 1 to 8;

R<sub>6</sub> and R<sub>7</sub> are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s),

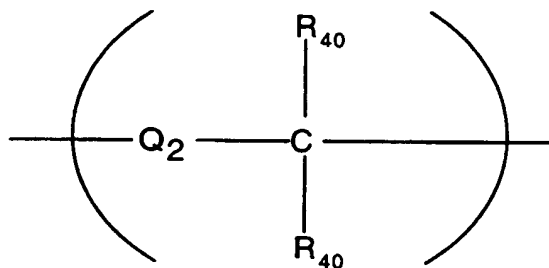


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heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

2. The compound of claim 1 wherein  $R_2$  is  
 5 hydrogen,  $C_1$ - $C_4$  alkyl,  $C_2$ - $C_4$  alkenyl,  $-O-(C_1$ - $C_3$  alkyl),  
 $-S-(C_1$ - $C_3$  alkyl),  $C_3$ - $C_4$  cycloalkyl,  $-CF_3$ , halo,  $-NO_2$ ,  $-CN$ , or  $-SO_3$ .

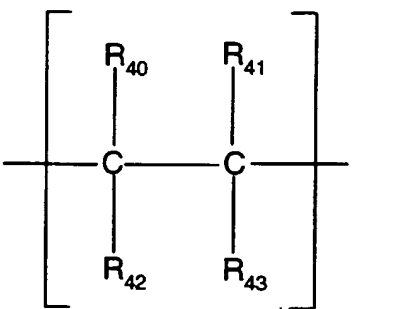
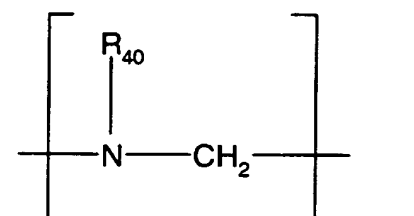
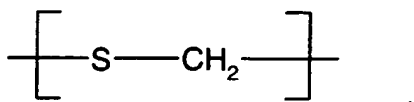
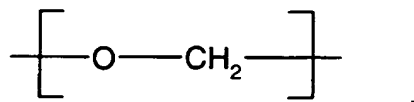
3. The compound of Claim 1 wherein the acylamino  
 10 acid linker group,  $-(L_C)-$ , for  $R_4$  is selected from a  
 group represented by the formula;



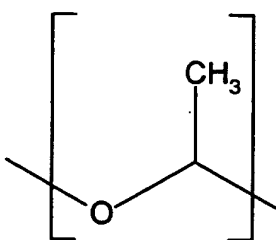
- 15 where  $Q_2$  is selected from the group  $-(CH_2)-$ ,  $-O-$ ,  $-NH-$ ,  
 $-C(O)-$ , and  $-S-$ , and each  $R_{40}$  is independently selected  
 from hydrogen,  $C_1$ - $C_8$  alkyl, aryl,  $C_1$ - $C_8$  alkaryl,  $C_1$ - $C_8$   
 alkoxy, aralkyl, and halo.

- 20 4. The compound of Claim 1 wherein the acylamino  
 acid linker group,  $-(L_C)-$ , for  $R_4$  selected from  $-(L_C)-$   
 is a divalent group selected from,

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or

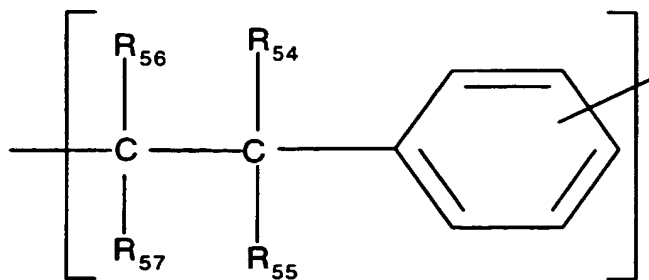
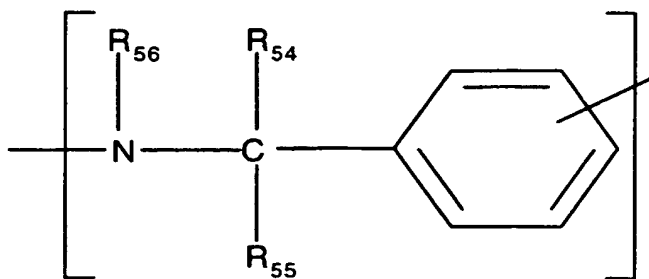
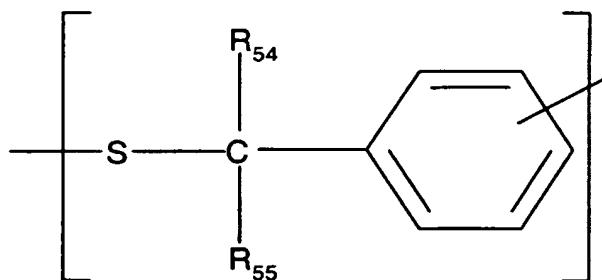
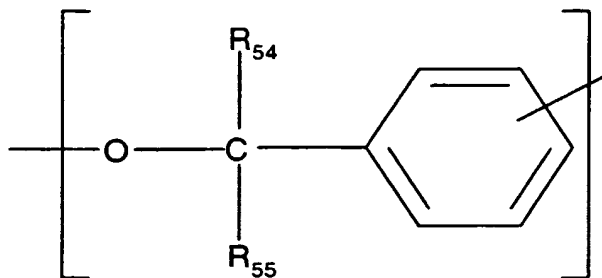


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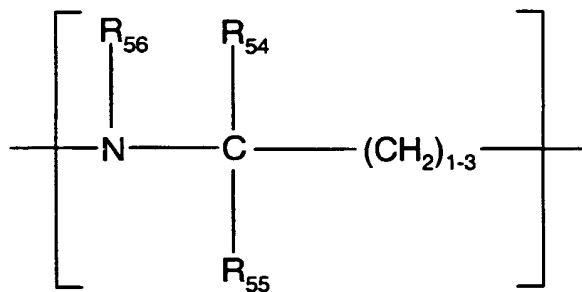
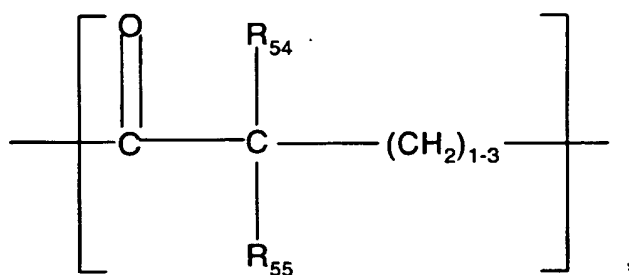
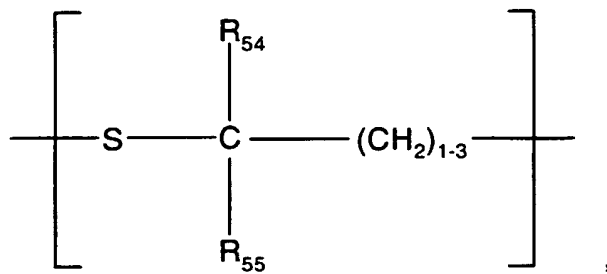
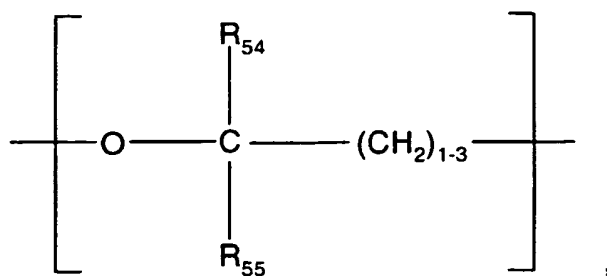
where R<sub>40</sub>, R<sub>41</sub>, R<sub>42</sub>, and R<sub>43</sub> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl.

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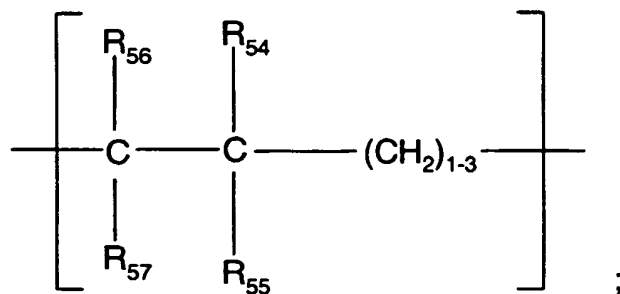
5. The compound of Claim 1 wherein the acid linker,  $-(L_a)-$ , for  $R_5$  is selected from a group represented by the formulae consisting of;



-116-



and



-117-

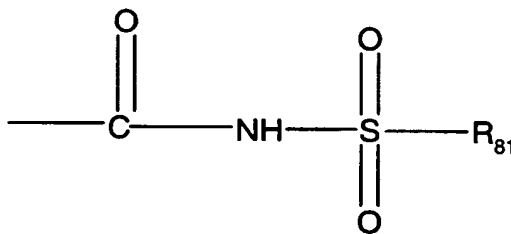
wherein R<sub>54</sub>, R<sub>55</sub>, R<sub>56</sub> and R<sub>57</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkoxy, or halo.

- 5            6. The compound of claim 1 wherein R<sub>5</sub> is the group, -(L<sub>a</sub>)-(acidic group) and wherein the (acidic group) is selected from the group:

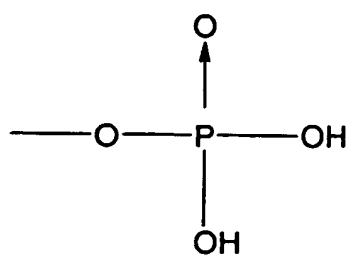
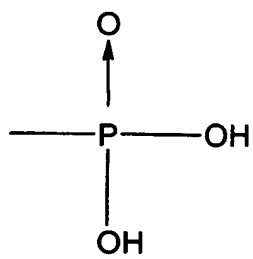
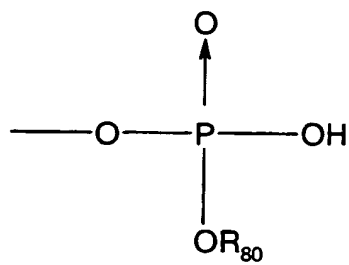
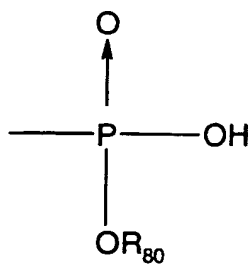
-5-tetrazolyl,

10

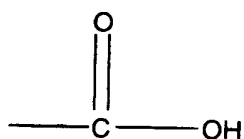
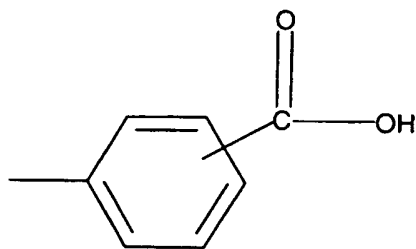
-SO<sub>3</sub>H,



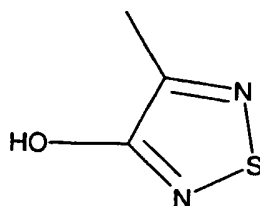
-118-



-119-

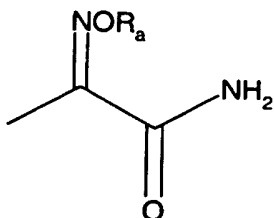


or



where  $R_{80}$  is a metal or  $C_1$ - $C_8$  alkyl and  $R_{81}$  is an organic substituent or  $-CF_3$ .

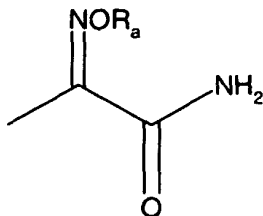
- 5            7. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



- and the linking group  $-(L_3)-$  is a bond; and  $R_a$  is  
 10 hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

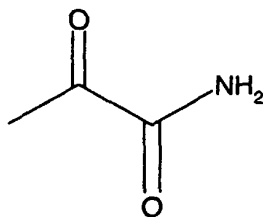
-120-

8. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



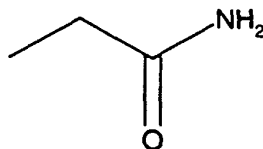
and the linking group  $-(L_3)-$  is a bond; and  $R_a$  is  
5 hydrogen.

9. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



10 and the linking group  $-(L_3)-$  is a bond.

10. The compound of claim 1 wherein for  $R_3$ , Z is the group represented by the formula;



15 and the linking group  $-(L_3)-$  is a bond.

11. The compound of Claim 1 wherein, for  $R_6$  the non-interfering substituent is hydrogen,  $C_1$ - $C_8$  alkyl,

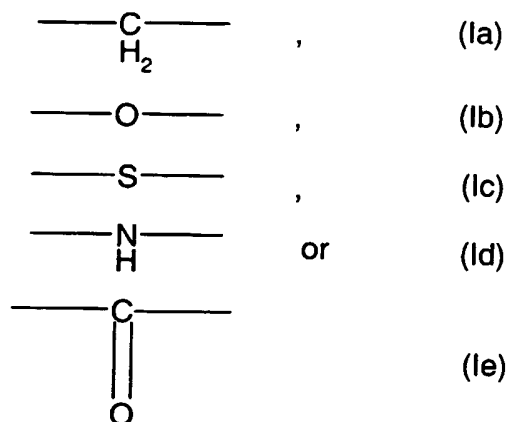


-121-

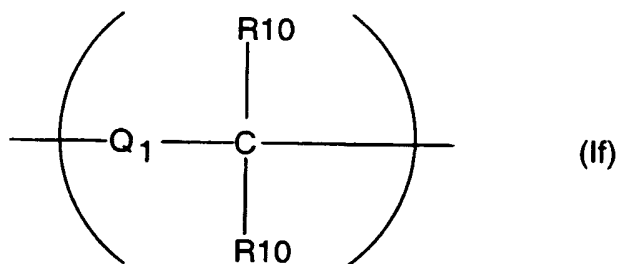
- C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>7</sub>-C<sub>12</sub> aralkyl, C<sub>7</sub>-C<sub>12</sub> alkaryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>2</sub>-C<sub>8</sub> alkenyloxy, C<sub>2</sub>-C<sub>8</sub> alkynyloxy, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyloxy, C<sub>2</sub>-C<sub>12</sub> alkylcarbonyl, C<sub>2</sub>-C<sub>12</sub> alkylcarbonylamino, C<sub>2</sub>-C<sub>12</sub> alkoxyamino, C<sub>2</sub>-C<sub>12</sub> alkoxyaminocarbonyl, C<sub>1</sub>-C<sub>12</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>2</sub>-C<sub>12</sub> alkylthiocarbonyl, C<sub>1</sub>-C<sub>8</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>8</sub> alkylsulfonyl, C<sub>2</sub>-C<sub>8</sub> haloalkoxy, C<sub>1</sub>-C<sub>8</sub> haloalkylsulfonyl, C<sub>2</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, -C(O)O(C<sub>1</sub>-C<sub>8</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>-O-(C<sub>1</sub>-C<sub>8</sub> alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO<sub>2</sub>R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH<sub>2</sub>)<sub>n</sub>-CO<sub>2</sub>H, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO<sub>3</sub>H, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

12. The compound of Claim 1 wherein for R<sub>1</sub> the divalent linking group -(L<sub>1</sub>)- is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):

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or

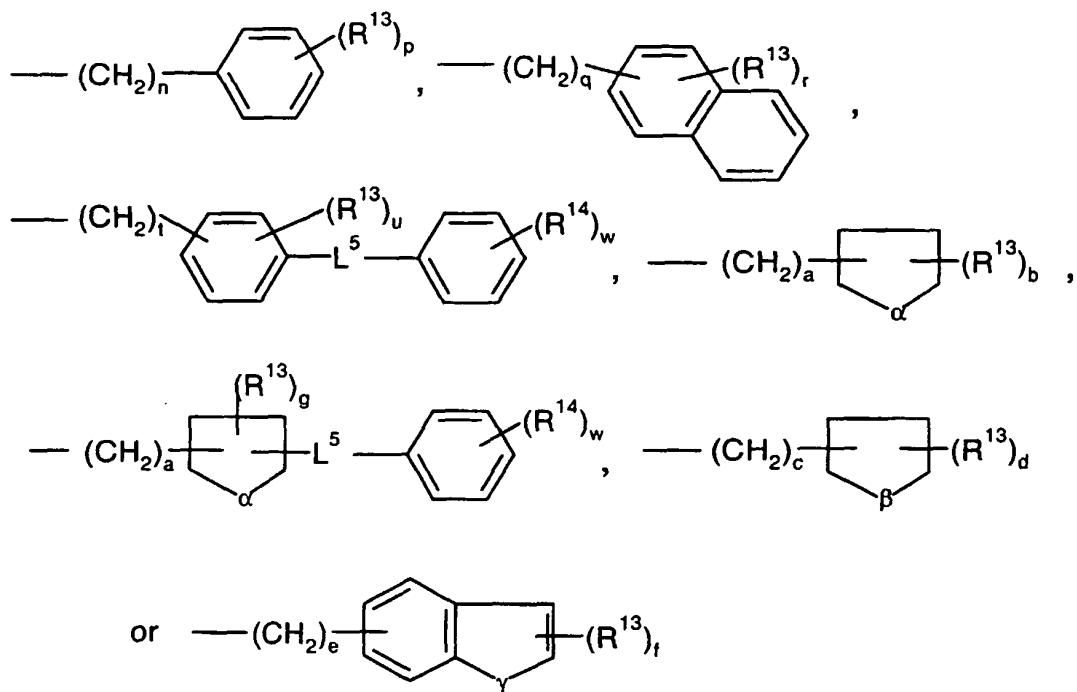


- 5 where Q<sub>1</sub> is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and R<sub>10</sub> is independently -H, C<sub>1-8</sub> alkyl, C<sub>1-8</sub> haloalkyl or C<sub>1-8</sub> alkoxy.

13. The compound of claim 1 wherein the linking  
 10 group -(L<sub>1</sub>)- of R<sub>1</sub> is -(CH<sub>2</sub>)- or -(CH<sub>2</sub>-CH<sub>2</sub>)-.

14. The compound of claim 1 wherein the linking  
 group -(L<sub>11</sub>)- of R<sub>11</sub> is a bond and R<sub>11</sub> is -(CH<sub>2</sub>)<sub>m</sub>-R<sup>12</sup>  
 wherein m is an integer from 1 to 6, and R<sup>12</sup> is a group  
 15 represented by the formula:

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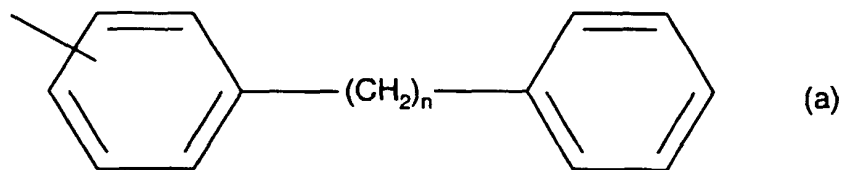


wherein a, c, e, n, q, and t are independently an integer from 0 to 2,  $R^{13}$  and  $R^{14}$  are independently selected from a halogen,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$  alkyloxy,  $C_1$  to  $C_8$  alkylthio, aryl, heteroaryl, and  $C_1$  to  $C_8$  haloalkyl,  $\alpha$  is an oxygen atom or a sulfur atom,  $L^5$  is a bond,  $-(CH_2)_v-$ ,  $-C=C-$ ,  $-CC-$ ,  $-O-$ , or  $-S-$ , v is an integer from 0 to 2,  $\beta$  is  $-CH_2-$  or  $-(CH_2)_2-$ ,  $\gamma$  is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group

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consisting of C<sub>1</sub> to C<sub>6</sub> alkyl, C<sub>1</sub> to C<sub>8</sub> alkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyloxy, C<sub>1</sub> to C<sub>8</sub> haloalkyl, aryl, and a halogen..

15. The compound of claim 1 wherein for R<sub>1</sub> the  
5 group R<sub>11</sub> is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl,  
10 diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzyl and related bibenzyl homologues represented by the formula (a):

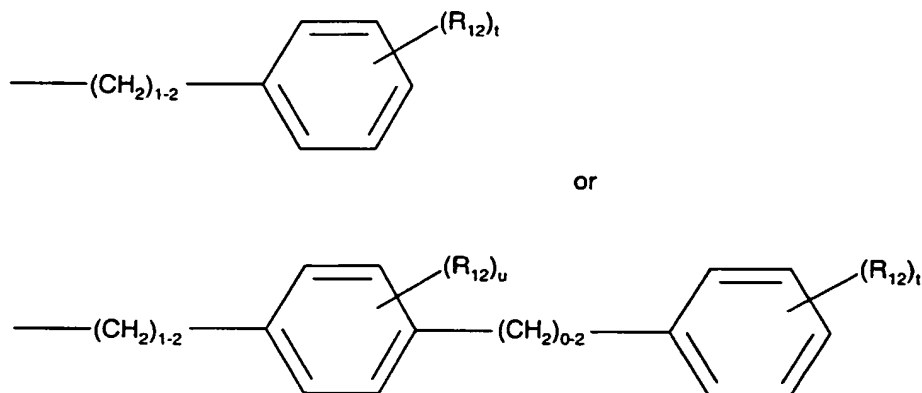


where n is a number from 1 to 8.

15

16. The compound of Claim 12 wherein for R<sub>1</sub> the combined group  $-(L_1)-R_{11}$  is selected from the groups;

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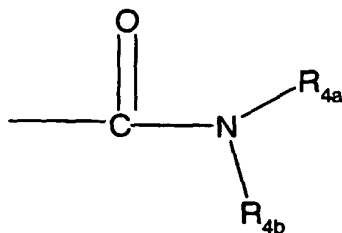
where  $R_{12}$  is a radical independently selected from halo,  $C_1$ - $C_{10}$  alkyl,  $C_1$ - $C_{10}$  alkoxy,  $-S-(C_1-C_{10} \text{ alkyl})$ , and  $C_1$ -  
 5  $C_{10}$  haloalkyl,  $C_1$ - $C_{10}$  hydroxyalkyl and  $t$  is a number from 0 to 5 and  $u$  is a number from 0 to 4.

17. The compound of claim 1 wherein for  $R_1$  the radical  $R_{11}$  is a substituted or unsubstituted  
 10 heterocyclic radical selected from pyrrolyl, pyrrolodinyll, piperidinyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl,  
 15 dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl,  
 20 pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl,

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quinazolinylmorpholino, thiomorpholino, homopiperazinyll,  
tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-  
dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,  
tetrahydrothiopheneyl, pentamethylenesulfadyl, 1,3-  
5 dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidinyll,  
hexamethyleneiminium, heptamethyleneiminium, piperazinyll  
or quinoxalinyll.

18. The compound of claim 1 wherein R<sub>4</sub> is the  
10 group, -(L<sub>C</sub>)-(acylamino acid group) and wherein the  
(acylamino acid group) is:

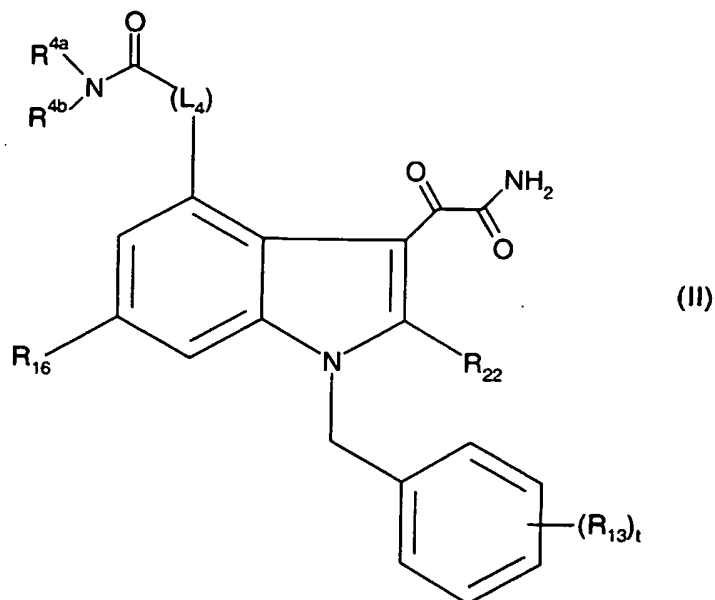


15 and R<sup>4a</sup> is selected from the group consisting of H, (C<sub>1</sub>-  
C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, heteroaryl and aryl; and wherein  
NR<sup>4b</sup> is an amino acid residue of a natural or unnatural  
amino acid with the nitrogen atom being part of the amino  
group of the amino acid.

20

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19. An indole compound represented by the formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof;



5

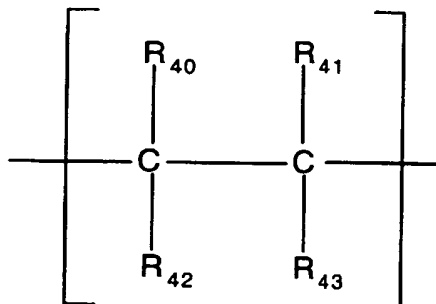
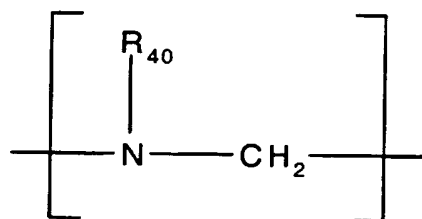
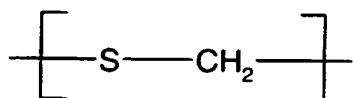
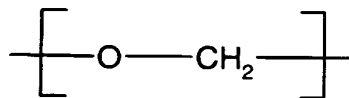
wherein ;

$R_{22}$  is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF<sub>3</sub>, -Cl, -Br, or -O-CH<sub>3</sub>;

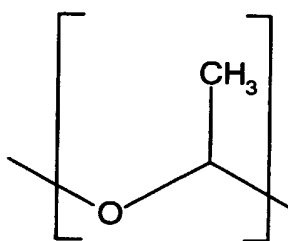
$R^{4a}$  is hydrogen; and

$NR^{4b}$  is an amino acid residue of a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid, and  $-(L_C)-$  is a divalent group selected from;

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or



5

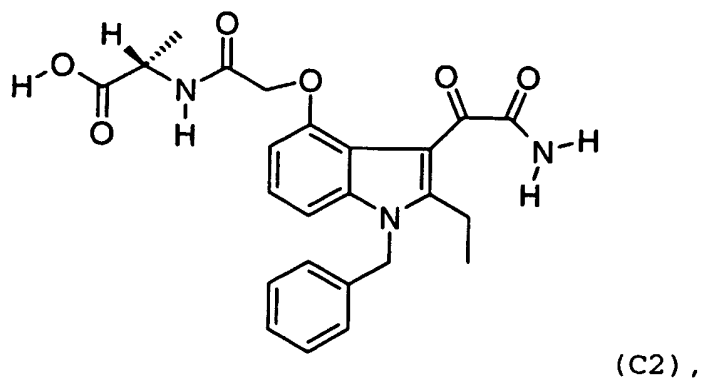
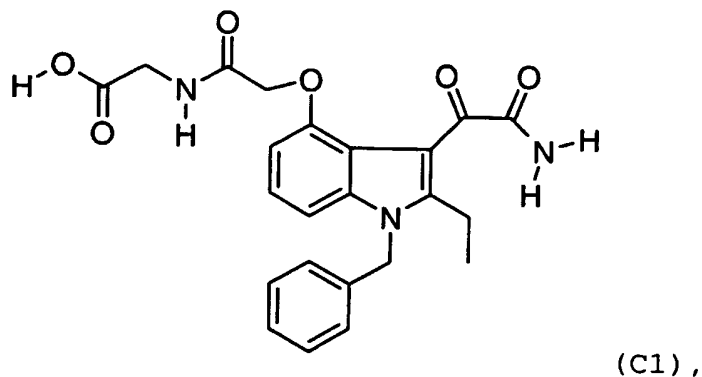
where  $\text{R}_{40}$ ,  $\text{R}_{41}$ ,  $\text{R}_{42}$ , and  $\text{R}_{43}$  are each independently selected from hydrogen or  $\text{C}_1$ - $\text{C}_8$  alkyl.



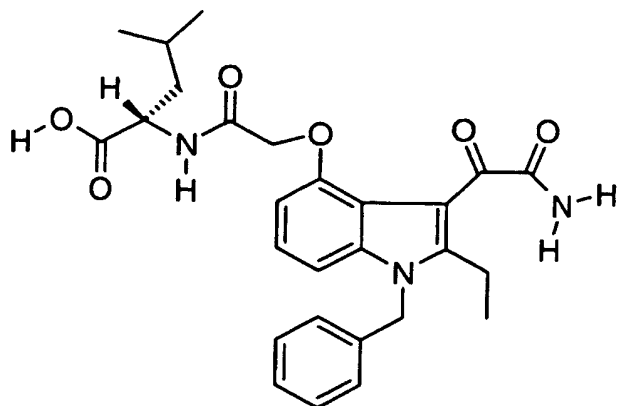
R<sub>16</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>8</sub> alkylthio C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, and halo.

R<sub>13</sub> is selected from hydrogen and C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxy, -S-(C<sub>1</sub>-C<sub>8</sub> alkyl), C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, phenyl, halophenyl, and halo, and t is an integer from 0 to 5.

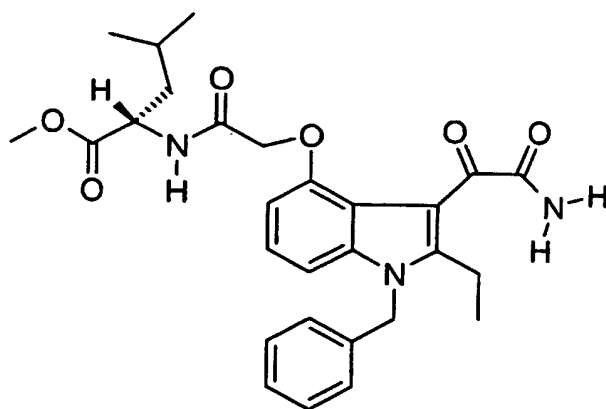
20. An indole compound represented by the formulae  
10 (C1), (C2), (C3), (C4), (C5), (C6), (C7), (C8), (C9),  
(C10) or (C11);



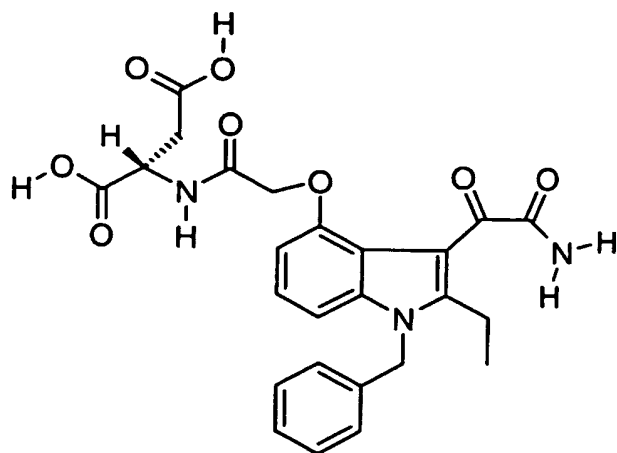
-130-



(C3) ,

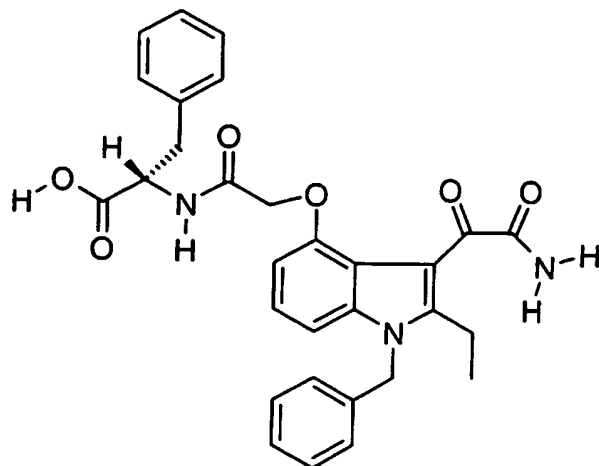


(C4) ,

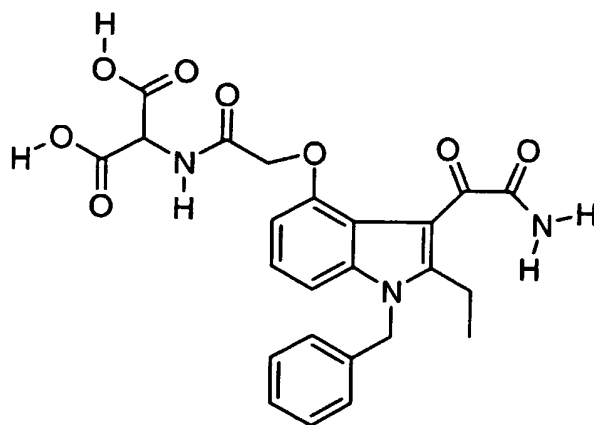


(C5) ,

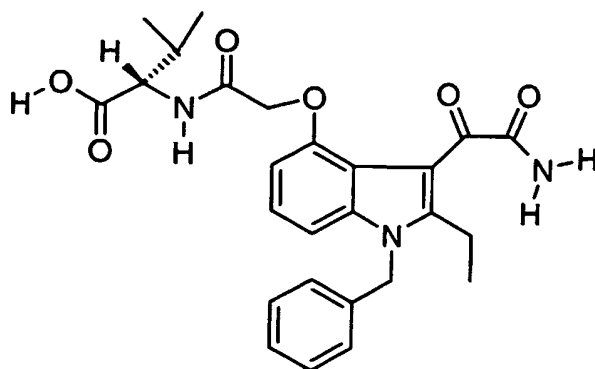
-131-



(C6) ,

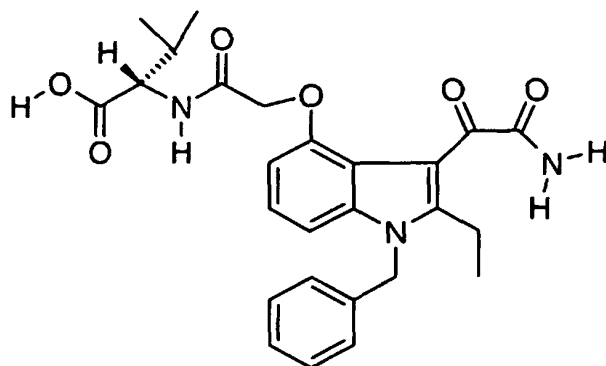


(C7) ,

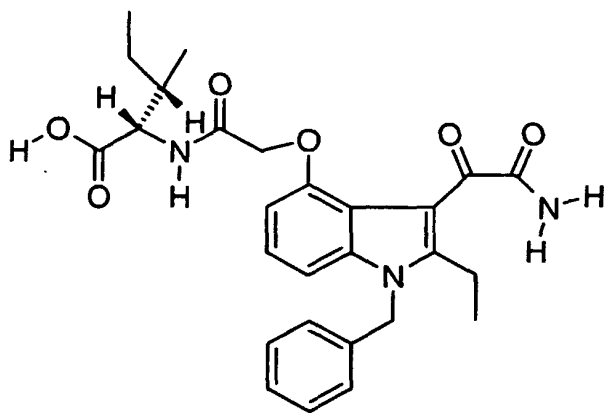


(C8) ,

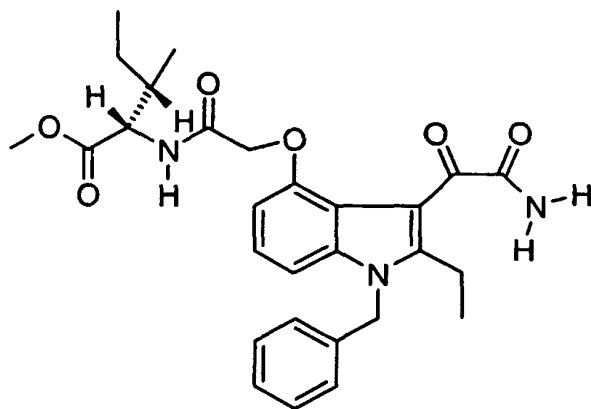
-132-



(C9) ,



(C10) and



(C11)

or pharmaceutically acceptable salts or prodrugs thereof.

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21. A compound of claim 1 selected from the group consisting of:

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

5        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

10        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

15        [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-  
indol-4-yl]oxy]acetamido]malonic acid;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-valine;

20        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-valine;

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*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

*N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

5        *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-  
1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

22. A pharmaceutical formulation comprising a indole  
compound as claimed in claim 1 together with a  
10 pharmaceutically acceptable carrier or diluent therefor.

23. A method of inhibiting sPLA<sub>2</sub> mediated release  
of fatty acid which comprises contacting sPLA<sub>2</sub> with a  
therapeutically effective amount of indole compound as  
15 claimed in claim 1.

24. A method of treating a mammal, including a  
human, to alleviate the pathological effects of  
Inflammatory Diseases; wherein the method comprises  
20 administration to said mammal of at least one indole  
compound as claimed in Claim 1 in a pharmaceutically  
effective amount.

25. A compound of claim 1 or a pharmaceutical  
25 formulation containing an effective amount of the

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compound of claim 1 in treatment of Inflammatory Diseases.

26. A compound of claim 1 or a pharmaceutical  
5 formulation containing an effective amount of the  
compound of claim 1 for use as an inhibitor for  
inhibiting sPLA<sub>2</sub> mediated release of fatty acid.

27. Use of a pharmaceutical composition comprising  
10 sPLA<sub>2</sub> inhibitor compounds according to Claim 1 and  
mixtures thereof for the manufacture of a medicament for  
the therapeutic treatment of Inflammatory Diseases.



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16319

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C07D209/22 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 675 110 A (LILLY CO ELI) 4 October 1995 (1995-10-04) cited in the application the whole document ---	1-26
Y	EP 0 620 215 A (LILLY CO ELI) 19 October 1994 (1994-10-19) cited in the application the whole document ---	1-26
Y	US 5 684 034 A (BACH NICHOLAS J ET AL) 4 November 1997 (1997-11-04) cited in the application the whole document --- -/--	1-26

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
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 Fax: (+31-70) 340-3016

Authorized officer

Frelon, D

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16319

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 00 37358 A (BACH NICHOLAS JAMES ; MORIN JOHN MICHAEL JUNIOR (US); LIN HO SHEN ( ) 29 June 2000 (2000-06-29) the whole document ---	1-26
Y	WO 99 21559 A (DENNEY MICHAEL LYLE ; MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ---	1-26
Y	WO 99 21546 A (DENNEY MICHAEL LYLE ; MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ---	1-26
A, P	EP 0 952 149 A (LILLY CO ELI) 27 October 1999 (1999-10-27) the whole document ---	
A	WO 96 37469 A (MERCK FROSST CANADA INC ; LAU CHEUK K (CA); BLACK CAMERON (CA); GUA) 28 November 1996 (1996-11-28) abstract; claims ---	1-26
A	WO 91 06537 A (AMERICAN HOME PROD) 16 May 1991 (1991-05-16) abstract; claims ---	1-26
A	DILLARD R D ET AL: "INDOLE INHIBITORS OF HUMAN NONPANCREATIC SECRETORY PHOSPHOLIPASE A21. INDOLE-3-ACETAMIDES" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 39, no. 26, 20 December 1996 (1996-12-20), pages 5119-5136, XP002046054 ISSN: 0022-2623 the whole document -----	1-26

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1-18 relate to an extremely large number of possible compounds. Unlimited and/or unspecified expressions like carbocyclic radical, heterocyclic radical, non-interfering substituents, a group containing 1 to 4 non-hydrogen atoms, a divalent linking group, aryl, aralkyl, acylamino acid, an acidic group or an organic substituents contain so many options, variables and possible permutations that the claims lack clarity and conciseness within the meaning of Article 6 PCT and arise to such an extent that a meaningful search of claims 1-18 is impossible. These claims have been therefore uncompletely searched.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the search is complete for claim 19 and dependent claims thereon on the basis of the illustrations by the examples wherein the following features appear constantly : R1 = benzyl; R2 = ethyl; R3 = CO-CO-NH2; R5,R6,R7 = H; R4 = O-CH2-CONH-aminoacid.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Interd 1al Application No

PCT/US 00/16319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921559 A		EP 1039911 A	04-10-2000
WO 9921546 A	06-05-1999	AU 1279899 A	17-05-1999
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		FI 921865 A	24-04-1992
		HU 63407 A	30-08-1993
		JP 5502222 T	22-04-1993
		PT 95692 A	13-09-1991
		US 5420289 A	30-05-1995
		US 5229516 A	20-07-1993

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>X-12420</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 16319</b>	International filing date (day/month/year) <b>11/07/2000</b>	(Earliest) Priority Date (day/month/year) <b>19/07/1999</b>
Applicant  <b>ELI LILLY AND COMPANY</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**SPLA2 INHIBITOREN**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1-18 relate to an extremely large number of possible compounds. Unlimited and/or unspecified expressions like carbocyclic radical, heterocyclic radical, non-interfering substituents, a group containing 1 to 4 non-hydrogen atoms, a divalent linking group, aryl, aralkyl, acylamino acid, an acidic group or an organic substituents contain so many options, variables and possible permutations that the claims lack clarity and conciseness within the meaning of Article 6 PCT and arise to such an extent that a meaningful search of claims 1-18 is impossible. These claims have been therefore uncompletely searched.

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/16319

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07D209/22 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Frelon, D



## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/16319

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 00 37358 A (BACH NICHOLAS JAMES ; MORIN JOHN MICHAEL JUNIOR (US); LIN HO SHEN ( ) 29 June 2000 (2000-06-29) the whole document ----	1-26
Y	WO 99 21559 A (DENNEY MICHAEL LYLE ; MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ----	1-26
Y	WO 99 21546 A (DENNEY MICHAEL LYLE ; MORIN JOHN MICHAEL JR (US); LILLY CO ELI (US)) 6 May 1999 (1999-05-06) the whole document ----	1-26
A, P	EP 0 952 149 A (LILLY CO ELI) 27 October 1999 (1999-10-27) the whole document ----	
A	WO 96 37469 A (MERCK FROSST CANADA INC ; LAU CHEUK K (CA); BLACK CAMERON (CA); GUA) 28 November 1996 (1996-11-28) abstract; claims ----	1-26
A	WO 91 06537 A (AMERICAN HOME PROD) 16 May 1991 (1991-05-16) abstract; claims ----	1-26
A	DILLARD R D ET AL: "INDOLE INHIBITORS OF HUMAN NONPANCREATIC SECRETORY PHOSPHOLIPASE A21. INDOLE-3-ACETAMIDES" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 39, no. 26, 20 December 1996 (1996-12-20), pages 5119-5136, XP002046054 ISSN: 0022-2623 the whole document -----	1-26

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0675110 A	04-10-1995	AU 688458 B	12-03-1998
		AU 1621795 A	12-10-1995
		BR 9501404 A	05-03-1996
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		CN 1114310 A	03-01-1996
		CZ 9500822 A	13-12-1995
		FI 951553 A	02-10-1995
		HU 72048 A	28-03-1996
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		NO 951252 A	02-10-1995
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921559 A		EP 1039911 A	04-10-2000
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WO 9106537 A	16-05-1991	AU 643996 B AU 7740491 A BR 9007790 A CA 2070422 A CA 2090042 A EP 0502106 A FI 921865 A HU 63407 A JP 5502222 T PT 95692 A US 5420289 A US 5229516 A	02-12-1993 31-05-1991 15-09-1992 28-04-1991 28-04-1991 09-09-1992 24-04-1992 30-08-1993 22-04-1993 13-09-1991 30-05-1995 20-07-1993

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

**RECEIVED**

To:  
  
GINAH, Francis O.  
ELI LILLY AND COMPANY  
Lilly Corporate Center  
Indianapolis, Indiana 46285  
ETATS-UNIS D'AMERIQUE

JUL 05 2001

ELI LILLY & COMPANY  
PATENT DIVISION

**PCT**

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year) 28.06.2001

Applicant's or agent's file reference  
X-12420

## IMPORTANT NOTIFICATION

International application No  
PCT/US00/16319

International filing date (day/month/year)  
11/07/2000

Priority date (day/month/year)  
19/07/1999

Applicant  
ELI LILLY AND COMPANY et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

H.S.

Name and mailing address of the IPEA/

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Fax. +49 89 2399 - 4465

Authorized officer

Ambroa, J.R.

Tel +49 89 2399-8012





# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>X-12420</b>		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/US00/16319</b>	International filing date (day/month/year) <b>11/07/2000</b>	Priority date (day/month/year) <b>19/07/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D209/22</b>		
Applicant <b>ELI LILLY AND COMPANY et al</b>		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 136 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input checked="" type="checkbox"/> Certain documents cited</li> <li>VII <input checked="" type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>		
Date of submission of the demand  <b>19/01/2001</b>		Date of completion of this report  <b>28.06.2001</b>
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel +49 89 2399 - 0 Tx. 523656 epmu d</b> <b>Fax +49 89 2399 - 4465</b>		Authorized officer  <b>Feiler, L</b>  Telephone No <b>+49 89 2399 8282</b> 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/16319

**I. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-109 as received on 13/06/2001 with letter of 11/06/2001

**Claims, No.:**

1-26 as received on 13/06/2001 with letter of 11/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/16319

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:  
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-18, 21-26.

because:

☒ the said international application, or the said claims Nos. 22, 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-18, 21, 24-26.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	19, 20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	19, 20
Industrial applicability (IA)	Yes:	Claims	19, 20

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/16319

---

No: Claims

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/16319

1. With letter of 11/06/01 the Applicant has filed a "replacement application comprising description pages 1-109 and Claims 1-26. It would appear that these documents do not indicate the amendments indicated in the response to the written opinion dated 16/03/00; they are essentially identical to the document originally filed.

2. Claims 22 and 23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

It has to be stressed that subject matter of Claims 1-18 has not been searched completely. Consequently, the following observations apply to **subject matter of Claim 19** and dependent claims only.

**3. Cited Documents**

EP-A-0675110= D1

EP-A-0620215= D2

US-A-5684034= D3

WO-A-0037358= D4

WO-A-9921559= D5

WO-A-9921546= D6

EP-A-0952149= D7

WO-A-9637469= D8

WO-A-9106537= D9

J. Med. Chem. 39(1996), pp. 5119-5139= D10

The indicated designation will be used throughout the examination procedure.

D4 and D7 are P-documents.

**4. Novelty**

The subject-matter of Claim 19 differs from D1 essentially due to the fact that the 4-position of the indole moiety is substituted by an acidic group (e.g. -COOH) whereas the corresponding position of the compounds of Claim 19 of the application comprises a carbamoyl group.

D2, D3 and D6 disclose indole-3-acetamid derivatives whereas the compounds of Claim 19 of the application are indole-3-glyoxylamides.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/US00/16319

According to D4 the 3-indole substituent is an oxime amide or oxime thioamide. D5 refers to a specific indol-4-yloxyacetic morpholino-N-ethylester.

D7 discloses carbazole derivatives, D8 refers to N-benzylindol-3-yl propanoic acid, D10 discloses indole-3-acetamides and D9 comprises indole derivatives not considered according to the application.

The subject-matter claimed can therefore be considered novel.

## **5. Inventive Step - Breadth of Claims**

### **5.1 Subjective Problem**

According to the application (p. 1, first paragraph and page 2, lines 14-16) the problem underlying the invention is to be seen in the provision of further compounds which are inhibitors of mammalian secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) and are therefore useful to treat inflammatory diseases.

### **5.2 Relevant and closest prior art**

Documents D1-D3, D5, D6, D9 and D10 are considered to be relevant for the assessment of inventive step since these compounds come structurally close to those comprised by Claim 19 of the application and also have the same qualitative activity. If the claimed priority date is not valid D4 may also come into picture.

The closest prior art is given by D1.

### **5.3 Objectively solved problem**

The application documents disclose the test methodology and quantitative test data according to the table of page 109 so that it can be said that at least the tested compounds solve the problem defined above.

### **5.4 Evaluation of the solution of the problem**

D1-D3, D5, D6, D9 and D10 disclose compounds structurally very similar to those of the present application.

The products of those documents also solve the problem of providing compounds which inhibit mamalian sPLA<sub>2</sub>.

The person skilled in the art seeking a solution to the problem defined above would therefore have been prompted to consider further derivatives of compounds which are already known to solve the above defined problem. In this context it is to be stressed that e.g. D1 discloses that the R<sup>4</sup> corresponding substituent is an acidic group e.g. the -COOH group, but D5 and D6 disclose that this group can be derivatised (ester functions) without changing the qualitative activity. In other words the compounds of D5

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/US00/16319

and D6 could be considered as prodrugs of D1-compounds. Consequently, the compounds of the invention being amide derivatives are to be considered as further prodrugs of D1-compounds.

The person skilled in the art would have been able to infer that a modification of the proposed type would have no effect on the activity profile so that he would have considered the proposed solution in the expectation of success.

The solution of the technical problem defined in point 5.1 according to the application is therefore obvious in the light of the prior art and thus the subject-matter of the present Claim 19 cannot be considered to be inventive.

#### **6. Industrial applicability**

For the assessment of the present claims 22 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### **7. Clarity**

- In Claim 19 ( $L_4$ ) remains undefined
- Claim 20 appears twice; specific compounds are claimed in the second Claim 20 already claimed in the first one; this is considered to be superfluous and should be avoided.
- Claim 24 is unclear.

#### **8. Suggestions**

In a possible national or regional examination procedure an inventive step could possibly be acknowledged should comparative data be submitted which show that apart from the technical problem defined in point 4.1 another, e.g. more exacting, problem, which can be derived from the application as originally filed (e.g. surprising improvement), existed and has actually been solved by originally disclosed technical

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/US00/16319

features, which would need to be incorporated in Claim 19.

In this respect it should be borne in mind that the compounds of the closest prior D1 must bear the closest possible structural resemblance in order that the comparison be valid. A suitable comparison would be e.g.:

Examples 1 and 17 of D1 versus corresponding compounds of the application whereby all possible variations should be included.

The breadth of the claims should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based.

Even if it turns out that the tested compounds of page 109 solve the problem defined in point 8, first paragraph the proposed broadness goes far beyond of what could be considered to be a reasonable generalisation:

$L_4$  is always  $-OCH_2-$ ;

$R_b$  is the residue of simple amino acids only;

$(R_{13})_1$  is always H;

$R_{16}$  is H and

$R^{22}$  is an alkyl only.

It is not reasonable e.g. to define  $NR_b$  as "an amino acid residue of a natural or unnatural amino acid" or to define  $L_4$  (which was obviously intended to mean (Lc)) other than  $-OCH_2-$ .

The description should be adapted to new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by Claim 1 are to be deleted.

All the documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.

172

10/018,037

10018037

Page 1

08/18/2002

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:sssptal626gms

PASSWORD:

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NEWS 1 Web Page URLs for STN Seminar Schedule - N. America  
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NEWS 3 Apr 09 BEILSTEIN: Reload and Implementation of a New Subject Area  
NEWS 4 Apr 09 ZDB will be removed from STN  
NEWS 5 Apr 19 US Patent Applications available in IFICDB, IFIPAT, and IFIUDB  
NEWS 6 Apr 22 Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS  
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER  
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available  
NEWS 9 Jun 03 New e-mail delivery for search results now available  
NEWS 10 Jun 10 MEDLINE Reload  
NEWS 11 Jun 10 PCTFULL has been reloaded  
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment  
NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;  
saved answer sets no longer valid  
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY  
NEWS 15 Jul 30 NETFIRST to be removed from STN  
NEWS 16 Aug 08 CANCERLIT reload  
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN  
NEWS 18 Aug 08 NTIS has been reloaded and enhanced  
NEWS 19 Aug 09 JAPIO to be reloaded August 18, 2002  
  
NEWS EXPRESS February 1 CURRENT WINDOWS VERSION IS V6.0d,  
CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),  
AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002  
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DICTIONARY FILE UPDATES: 16 AUG 2002 HIGHEST RN 444143-26-4

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Please note that search-term pricing does apply when  
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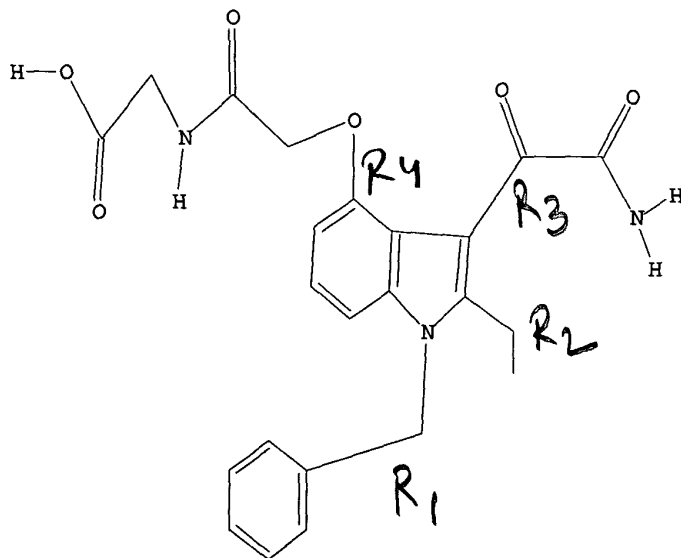
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Calculated physical property data is now available. See HELP PROPERTIES  
for more information. See STNote 27, Searching Properties in the CAS  
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=>  
Uploading 10018037.str

L1 STRUCTURE UPLOADED

=> d l1  
L1 HAS NO ANSWERS  
L1 STR



Structure attributes must be viewed using STN Express query preparation.

Golam Shameem

=> s l1

SAMPLE SEARCH INITIATED 09:31:40 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS  
SEARCH TIME: 00.00.01

1 ANSWERS

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 9 TO 360  
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> FIL CAPLUS

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
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L1 STRUCTURE UPLOADED  
L2 1 S L1

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=> s l1

REGISTRY INITIATED  
Substance data SEARCH and crossover from CAS REGISTRY in progress...

Golam Shameem

Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

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SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS  
SEARCH TIME: 00.00.01

1 ANSWERS

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 9 TO 360  
PROJECTED ANSWERS: 1 TO 80

L3 1 SEA SSS SAM L1

L4 1 L3

=> FIL REGISTRY  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
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for more information. See STNote 27, Searching Properties in the CAS  
Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> s l1 sss full

FULL SEARCH INITIATED 09:32:31 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 164 TO ITERATE

100.0% PROCESSED 164 ITERATIONS  
SEARCH TIME: 00.00.01

8 ANSWERS

L5 8 SEA SSS FUL L1

=> FIL CAPLUS  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION

Golam Shameem



FULL ESTIMATED COST

140.28

142.05

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=&gt; s l5

L6

1 L5

=&gt; d ibib abs hitstr l6 tot

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:63970 CAPLUS

DOCUMENT NUMBER: 134:116236

TITLE: Preparation of indole amino acid derivatives as secretory phospholipase A2 (sPLA2) inhibitors

INVENTOR(S): Lin, Ho-Shen; Richett, Michael Enrico

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 142 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005761	A1	20010125	WO 2000-US16319	20000711
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

Golam Shameem

EP 1202963

A1 20020508

EP 2000-944673

20000711

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.:

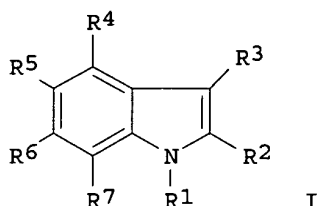
US 1999-144502P P 19990719

WO 2000-US16319 W 20000711

OTHER SOURCE(S):

MARPAT 134:116236

GI



AB Indole derivs. I [R1 = (un)substituted alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, or heterocyclyl connected directly or via a divalent linking group to the indole ring; R2 is H or a group contg. 1-4 non-hydrogen atoms plus any required hydrogen atoms; R3 is -L3-Z, where L3 is a bond, CH2, O, S, NH, or CO and Z is -C(:NORa)C(:X)NH2, -C(:X)CONH2, or CRa2C(:X)NH2 (X = O or S and Ra = alkyl, aryl, alkaryl, alkoxy, aralkyl, CN); R4 is the group -(Lc)-(acylamino acid group), where Lc is an acylamino acid linker; R5 is H, a non-interfering substituent, or the group -(La)-(acidic group), where La is an acid linker; R6, R7 = H, a non-interfering substituent or (un)substituted carbocyclyl] were prep'd. for inhibiting sPLA2 mediated release of fatty acids for treatment of inflammatory diseases such as septic shock. Thus, treatment of N-tert-butoxycarbonyl-3-methoxy-2-methylaniline with N-methoxy-N-methylpropanamide and then trifluoroacetic acid afforded 2-ethyl-4-methoxy-1H-indole. N-benzylation, O-demethylation, alkylation with Me bromoacetate, reaction with oxalyl chloride and ammonia gave [[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid Me ester (1). Reaction of 1 with glycine Me ester hydrochloride and sapon. afforded N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine (3a). Compds. 1 and 3a resp. showed IC50 = 49 and 71 nM for inhibition of human secreted PLA2.

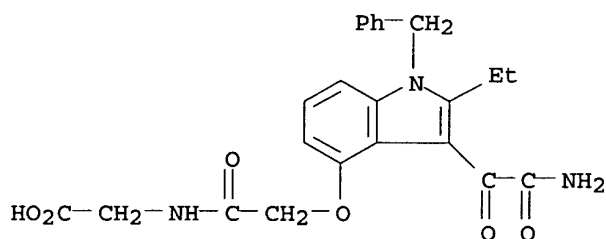
IT 321153-17-7P 321153-19-9P 321153-21-3P  
321153-23-5P 321153-25-7P 321153-27-9P  
321153-29-1P 321153-31-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of indole amino acid derivs. as secretory phospholipase A2 (sPLA2) inhibitors)

RN 321153-17-7 CAPLUS

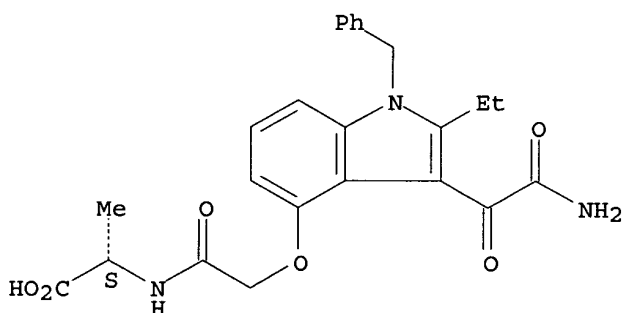
CN Glycine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)



RN 321153-19-9 CAPLUS

CN L-Alanine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

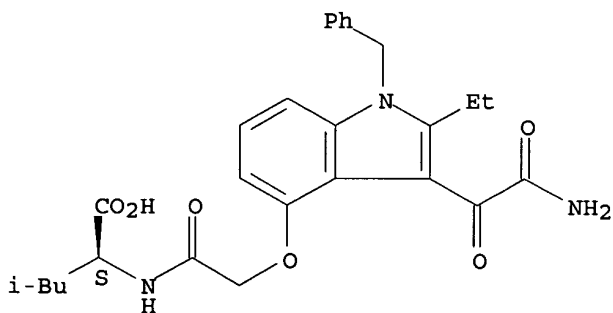
Absolute stereochemistry.



RN 321153-21-3 CAPLUS

CN L-Leucine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

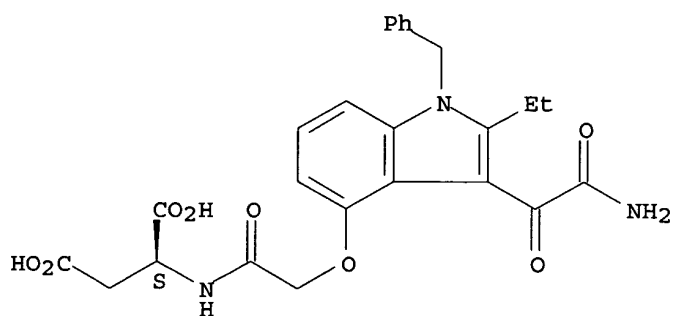
Absolute stereochemistry.



RN 321153-23-5 CAPLUS

CN L-Aspartic acid, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

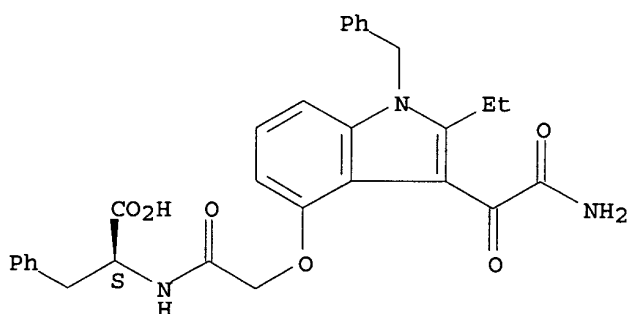
Absolute stereochemistry.



RN 321153-25-7 CAPLUS

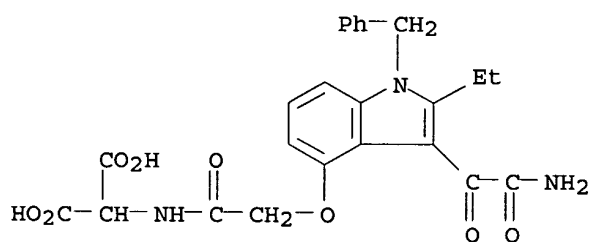
CN L-Phenylalanine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 321153-27-9 CAPLUS

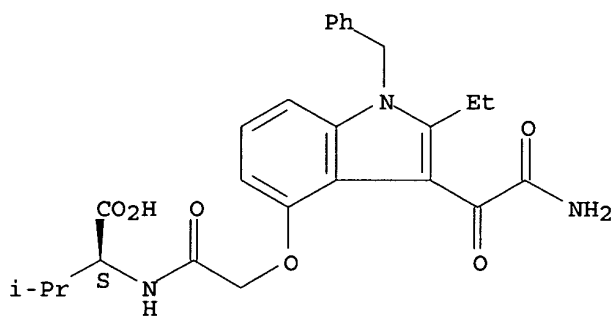
CN Propanedioic acid, [[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]amino]- (9CI) (CA INDEX NAME)



RN 321153-29-1 CAPLUS

CN L-Valine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

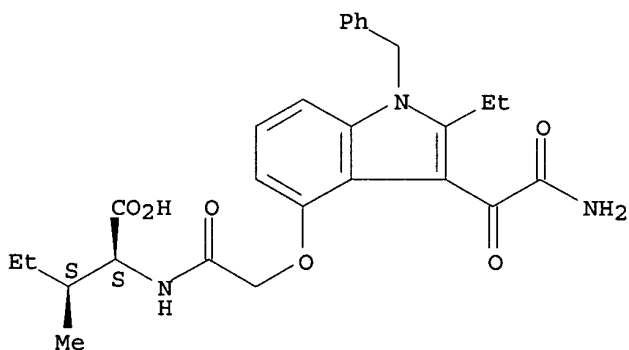
Absolute stereochemistry.



RN 321153-31-5 CAPLUS

CN L-Isoleucine, N-[[[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS

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FULL ESTIMATED COST

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147.63

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Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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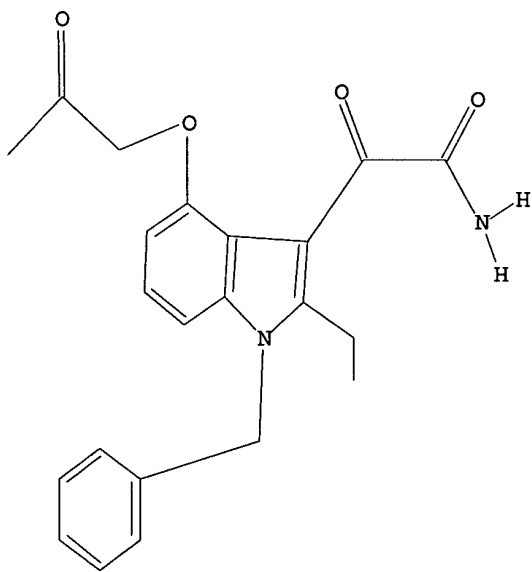
Uploading 10018037a.str

L7 STRUCTURE UPLOADED

=> d 17

L7 HAS NO ANSWERS

L7 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 17

SAMPLE SEARCH INITIATED 09:34:49 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS  
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:	ONLINE	**COMPLETE**
	BATCH	**COMPLETE**
PROJECTED ITERATIONS:	9 TO	360
PROJECTED ANSWERS:	0 TO	0

0 ANSWERS

L8 0 SEA SSS SAM L7

=> s 17 sss full

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FULL SEARCH INITIATED 09:35:05 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 164 TO ITERATE

100.0% PROCESSED 164 ITERATIONS  
SEARCH TIME: 00.00.01

0 ANSWERS

L9 0 SEA SSS FUL L7

=>

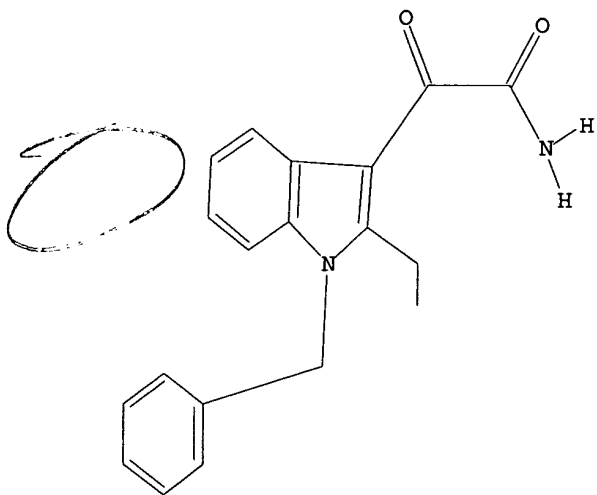
Uploading 10018037b.str

L10 STRUCTURE UPLOADED

=> d l10

L10 HAS NO ANSWERS

L10 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l10

SAMPLE SEARCH INITIATED 09:36:41 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 10 TO ITERATE

100.0% PROCESSED 10 ITERATIONS  
SEARCH TIME: 00.00.01

6 ANSWERS

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 11 TO 389  
PROJECTED ANSWERS: 6 TO 266

L11 6 SEA SSS SAM L10

=> s l10 sss full

FULL SEARCH INITIATED 09:36:51 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 209 TO ITERATE

Golam Shameem

100.0% PROCESSED 209 ITERATIONS  
SEARCH TIME: 00.00.01

136 ANSWERS

L12 136 SEA SSS FUL L10

= FILE CAPLUS  
COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
281.70	429.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
0.00	-0.62

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FILE LAST UPDATED: 16 Aug 2002 (20020816/ED)

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=&gt; d his

(FILE 'HOME' ENTERED AT 09:30:57 ON 18 AUG 2002)

FILE 'REGISTRY' ENTERED AT 09:31:16 ON 18 AUG 2002

L1 STRUCTURE UPLOADED  
L2 1 S L1

FILE 'CAPLUS' ENTERED AT 09:31:48 ON 18 AUG 2002  
S L1

L3 FILE 'REGISTRY' ENTERED AT 09:32:03 ON 18 AUG 2002  
1 S L1

L4 FILE 'CAPLUS' ENTERED AT 09:32:04 ON 18 AUG 2002  
1 S L3

L5 FILE 'REGISTRY' ENTERED AT 09:32:24 ON 18 AUG 2002  
8 S L1 SSS FULL

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FILE 'CAPLUS' ENTERED AT 09:32:38 ON 18 AUG 2002

L6 1 S L5

FILE 'REGISTRY' ENTERED AT 09:34:19 ON 18 AUG 2002

L7 STRUCTURE UPLOADED

L8 0 S L7

L9 0 S L7 SSS FULL

L10 STRUCTURE UPLOADED

L11 6 S L10

L12 136 S L10 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:37:05 ON 18 AUG 2002

=> s 12

L13 1150557 12

=> d ibib abs hitstr l13 1-20

L13 ANSWER 1 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618739 CAPLUS

TITLE: One-pot synthetic method of carbonothiolates:  
selenium-catalyzed reaction of alcohol, disulfide and carbon monoxide

AUTHOR(S): Yutaka, Nishiyama; Takeshi, Maehira; Junko, Nakase; Noboru, Sonoda

CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, 564-8680, Japan  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-346. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB The development of a convenient and efficient method for the synthesis of S-aryl and S-alkylcarbonothiolates has attracted considerable attention in org. synthesis. In this presentation we will describe a one-pot synthetic method of carbonothiolates by the reaction of alc., disulfide and carbon monoxide in the presence of a catalytic amt. of selenium. When ethanol was allowed to react with di-Ph disulfide in the presence of a catalytic amt. of selenium (0.1equiv.) and an excess amt. of triethylamine as a base in THF solvent under the pressure of carbon monoxide (25 atm) at 25 °C for 6 h, S-phenyl-O-ethylcarbonothiolate was obtained in almost quant. yield. For ethanol, butanol and benzylalc., the corresponding S-phenyl-O-alkylcarbonothiolates were obtained in 100, 93, and 77 % yields, resp. In the case of secondary alc. like iso-propanol, the reaction was not completed under the same reaction conditions as that of primary alc. giving S-phenyl-O-i-propylcarbonothiolate in only 12 % yield. The yield of coupling product was improved by the reaction under harder reaction conditions (70 atm) at 80 °C for 13 h. Similarly, ethanol was reacted with various diaryl disulfides to give the corresponding S-aryl-O-methylcarbonothiolates in excellent to good yields. One-pot synthesis of S-alkyl-O-alkylcarbonothiolate by the selenium-catalyzed coupling reaction of alc., dialkyl disulfide and carbon monoxide was nextly examined. In the use of triethylamine as a tertiary amine, the yields of S-alkyl-O-alkylcarbonothiolates were very low; however, the yields were improved by the use of DBU as a base, S-alkyl-O-alkylcarbonothiolates were synthesized in moderate yields. In summary, selenium-catalyzed one-pot synthetic method of carbonothiolates

by the reaction of alc., disulfide and carbon has been developed.

L13 ANSWER 2 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:618670 CAPLUS  
TITLE: Pyrolysis of phenyl benzoate  
AUTHOR(S): Kidder, Michelle K.; Britt, Phillip F.; Buchanan, A. C., III  
CORPORATE SOURCE: Chemical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37831, USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-276. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English  
AB The thermal degrdn. of diaryl esters currently is of interest. However, the low temp. pyrolysis of diaryl esters has not been studied in great detail. Here the pyrolysis of Ph benzoate was studied neat and dild. in naphthalene at 400 .degree.C. The major products from the pyrolysis of the neat substrate were benzene, phenol, and benzoic acid, while smaller amts. of biphenyl, benzophenone, Ph biphenylcarboxylate, and Ph benzoylbenzoate were obsd. Surprisingly, the reaction rate increased ca. 30% when Ph benzoate was dild. 10-fold in naphthalene and 1- and 2-phenylnaphthalene (12.8 +/- 2.1 mol%) were formed at the expense of Ph biphenylcarboxylate. Although C-O homolysis (bond dissocn. energy=70 kcal/mol), should not occur to an appreciable extent at 400 .degree.C, these products indicate that Ph radicals are produced in the reaction. Ph radicals could be produced from the decompn. of benzoic anhydride, formed from the condensation of benzoic acids, but the addn. of water (10-20 mol%) reduced the formation of Ph biphenylcarboxylate ca. 40-58%. The mechanistic origins of the products will be discussed in the presentation.

L13 ANSWER 3 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:618658 CAPLUS  
TITLE: Advances in the asymmetric construction of architecturally complex natural products: The lituarines  
AUTHOR(S): Smith, Amos B., III; Frohn, Michael; Walsh, Shawn P.  
CORPORATE SOURCE: Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-264. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English  
AB The lituarines A, B, and C comprise a small class of highly complex, bioactive natural products isolated from the sea pen *Lituarina australasiae*. Recently we initiated efforts to develop a convergent, stereocontrolled synthesis of these novel macrolides. Early achievements include an efficient construction of (+)-2 via the 6-endo cyclization of an epoxy-alc. to access the C(8-12) tetrahydropyran ring and a kinetically controlled acid-catalyzed spiroketalization. Construction of (-)-3 via common precursor (-)-1 has also been achieved. A summary of these results, as well as addnl. progress will be presented.

L13 ANSWER 4 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

Golam Shameem

ACCESSION NUMBER: 2002:618624 CAPLUS  
TITLE: Mechanistic investigation of the olefin cyclopropanation reaction using (Salen)Ru(carbene) catalysts  
AUTHOR(S): Jing, Huanwang; Nguyen, SonBinh T.  
CORPORATE SOURCE: Department of Chemistry, Northwestern University, Evanston, IL, 60208-3113, USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-230. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English  
AB The cyclopropanation of styrene by several diazo-compds. R1R2CN2 (R1=H, R2=CO2Et (1, EDA); R1=H, R2=CO2tBu (2, tBDA); R1=H, R2=SiMe3 (3); R1=R2=phenyl (4); R1=H, R2=H (5); R1=H, R2=phenyl (6); and R1=CH3CO, R2=CO2Et (7)) using (Salen)Ru(PPh3)2 as catalyst (salen=1,2-ethanediamino-N,N'-bis(3,5-di-tert-butyl-salicylidene) (A); (S,S)-(+) -1,2-cyclohexanediamino-N,N'-bis(3,5-di-tert-butyl-salicylidene) (B, made in-situ); and 1,2-ethanediamino-N,N'-bis(salicylidene) (C)) were investigated. Although the formation of metal carbene complexes can be obsd. at room temp. for all reactions, the catalytic cyclopropanation of styrene occur only when EDA or tBDA is present. The reaction intermediates and metal carbene complexes were monitored by UV and 1H NMR spectroscopy. Interestingly, the stoichiometric reaction between carbene complexes and styrene do not lead to cyclopropane product. Reaction results between deuterated ethyldiazoacetate and styrene in the presence of a pre-formed ruthenium ethyldiazoacetate carbene complex only gave deuterated cyclopropane. These results suggested that the mechanism of cyclopropanation for our ruthenium salen system do not make use of either a carbene-transfer process or a bis-carbene transfer mechanism. Rather, the diazo-compd. coordinated carbene complex [(Salen)(R1R2N2)Ru=CR1R2] is proposed as an intermediate. The carbene complexes ((Salen)Ru=CHSiMe3) (3) and ((Salen)Ru=CPh2) (4) were prepd. and characterized by 1H and 13C NMR spectroscopy, FAB-MS, and elemental anal. The structure of carbene 4 was detd. by X-ray crystallog. Complex 4 crystallizes in triclinic cell with dimensions: a=11.409(2) .ANG., b=12.308(2) .ANG., c=16.032(3) .ANG., .alpha.=68.968(2).degree., .beta.=85.531(3).degree., .gamma.=70.416(2).degree., V=1977.4(5) .ANG.3, space group: P-1, Z=2, .rho. calcd=1.27 g/cm3.

L13 ANSWER 5 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618614 CAPLUS  
TITLE: Chelation-assisted C-H activation and its application in hydroesterification of unsaturated compounds and in doubly catalytic cross-coupling reactions  
AUTHOR(S): Chang, Sukbok; Ko, Sangwon; Na, Youngim; Han, Soobong; Kang, Byungman  
CORPORATE SOURCE: Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 305-701, S. Korea  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-220. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English  
AB An efficient and catalytic protocol of hydroesterification of unsatd.

comps. has been developed without a need of CO atm. With the introduction of 2-pyridyl moiety as a chelating group in formate, Ru<sub>3</sub>(CO)<sub>12</sub> catalyzed activation of formyl C-H bond of formate and subsequent addn. of the intermediate to alkenes and alkynes proceeds with almost complete suppression of decarbonylation. Stereoselectivity of the produced one carbon elongated esters was good to excellent for the formation of linear adduct depending on the bulkiness of the alkenes used. This procedure could be readily applied to a variety of olefins such as terminal, internal, cyclic, bicyclic, vinyl ether, and conjugated enone systems with high efficiency and selectivity. It could be also applied to hydroesterification of alkynes under the similar conditions. In addns., it was amenable to a solvent free condition with same efficiency. Based on the chelation driven C-H bond activation of formate, a putative mechanism of the Ru-catalyzed hydroesterification of 2-pyridylmethyl formate has been proposed. This method of Ru-catalyzed C-H activation could be combined with Pd-catalyzed cross-coupling reactions, in which aryl iodides were readily reacted with formates to give benzoates in high yields. This represents the first example of transition metal catalyzed transmetalation which could be potentially applied to a variety of coupling reactions.

L13 ANSWER 6 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:

2002:618601 CAPLUS

TITLE:

Hinged molecular capsules

AUTHOR(S):

Tunstad, Linda M.; Castro, Peter P.; Kang, Sang-Woo; Nunez, Jose; Zhao, Gang

CORPORATE SOURCE:

Department of Chemistry and Biochemistry, California State University Los Angeles, Los Angeles, CA, 90032, USA

SOURCE:

Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-207. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE:

Conference; Meeting Abstract

LANGUAGE:

English

AB

The synthesis, characterization, and conformational changes (based on VT 1H NMR) of two new bis-cavitand hosts based on resorcinarene macrocycles are reported. The nonconvergent bis-cavitand host "Z", possesses two different concave binding surfaces. The convergent bis-cavitand host "C" takes the shape of a capsule. According to CPK models this capsule possesses a cavity of 12-14 angstroms in length and 6-8 angstroms in width. The hosts are conformationally flexible, as evident by dynamic 1H NMR. Of particular interest to us is capsule "C", which has the potential to open and close (depending on temp.) to bind or release a guest in soln. The flexibility seems to be temp. as well as solvent dependent.

L13 ANSWER 7 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:

2002:618559 CAPLUS

TITLE:

Solid-phase synthesis of 2-aminobenzimidazoles via a polymer bound o-phenylenediamine intermediate

AUTHOR(S):

Arvanitis, Elena A.; Player, Mark R.

CORPORATE SOURCE:

Chemistry, 3-Dimensional Pharmaceuticals, Cranbury, NJ, 08512, USA

SOURCE:

Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-164. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB The synthesis of a 2-aminobenzimidazole library using Irori Microkans is described. Three points of diversity were introduced in the 2-aminobenzimidazole scaffold, 3. Reductive amination of the com. available 4-formyl-3,5-dimethoxypolystyrene resin, 1 followed by attachment of 4-fluoro-2-nitrobenzoic acid led to the polymer-bound o-phenylenediamine intermediate, 2 after arom. nucleophilic substitution of fluorine with primary amines or anilines and subsequent nitro-redn. Treatment with aryl or aroyl isothiocyanates in the presence of diisopropylcarbodiimide afforded the desired 2-aminobenzimidazoles 3, after cleavage from the support with 10% trifluoroacetic acid. This methodol. was utilized for the synthesis of a 12,000-member library.

L13 ANSWER 8 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618490 CAPLUS

TITLE: Synthesis and secondary structure of .beta.-peptides containing (3R)-amino-D-proline: Expansion of the monomer pool for .beta.-peptide library construction

AUTHOR(S): Porter, Emilie A.; Wang, Xifang; Schmitt, Margaret A.; Weisblum, Bernard; Gellman, Samuel H.

CORPORATE SOURCE: Dept. of Chemistry, University of Wisconsin, Madison, WI, 53706, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), ORGN-095. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB A synthesis to a new cationic .beta.-amino acid, (3R)-amino-D-proline (AP), was developed. .beta.-Peptides contg. AP were synthesized via solid-phase peptide synthesis and analyzed for helix formation. 2D-NMR and CD data suggest that these peptides display 12-helical secondary structure in methanol and water. In addn., a 17-residue .beta.-peptide contg. AP shows antibiotic activity. The design of new structure-inducing .beta.-amino acids is important, because a large monomer pool is desirable for the development of .beta.-peptide combinatorial libraries.

L13 ANSWER 9 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618393 CAPLUS

TITLE: Real-time elemental analysis of glass batch mixture by laser induced breakdown spectroscopy

AUTHOR(S): Lal, Banshi; Yueh, Fang-Yu; Singh, Jagdish P.; Ramsey, William G.

CORPORATE SOURCE: Diagnostic Instrumentation & Analysis Laboratory, Mississippi State University, Starkville, MS, 39759, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), NUCL-081. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Transmission, index of refraction, thermal consts., mechanical and chem. characteristics of glass are sensitive to the concn. of its constituents. A real-time direct monitoring of the constituent concn. of the mixt. used to manuf. glass can help in energy conservation besides redn. in the

wastage of raw constituents. Laser-induced breakdown spectroscopy (LIBS) technique is fast emerging as one of the best real-time diagnostic tool for elemental anal. primarily because of its short response time-results are available faster. In this study a glass batch mixt. consisting of  $\text{SiO}_2$ ,  $\text{Al}_2\text{O}_3$ ,  $\text{Na}_2\text{CO}_3$  and  $\text{CaCO}_3$  has been chosen for investigation. This mixt. is used to make window glass that has typical compn. of 71% $\text{SiO}_2$ , 1% $\text{Al}_2\text{O}_3$ , 12% $\text{Na}_2\text{O}$  and 16% $\text{CaO}$ . 532nm radiation from a frequency doubled pulsed Nd:YAG laser (Continuum Surelite I) is focused on the sample using a 500mm focal length, UV grade fused silica plano-convex lens which also collects emission from the laser induced spark produced at the focus. The emission from the spark is fed to a spectrometer (24001/mm grating, Spex 500M) through an optical fiber. The spectrometer is fitted with a gated 1024-element intensified diode array detector (Princeton Applied Research Model IDAD-1024). EG&G OMAVISION PC software is used for data acquisition and anal. The optimization of various parameters to get reproducible LIBS data is discussed in the paper.

L13 ANSWER 10 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618354 CAPLUS

TITLE: New results concerning heavy element synthesis

AUTHOR(S): Loveland, Walter D.; Gregorich, Ken; Ginter, T. N.;  
Ninov, V.; Patin, J. B.; Peterson, D.; Collaboration,  
SHEIKS

CORPORATE SOURCE: Department of Chemistry, Oregon State University,  
Corvallis, OR, 97331, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting,  
Boston, MA, United States, August 18-22, 2002 (2002),  
NUCL-042. American Chemical Society: Washington, D.  
C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB We report the confirmation of the synthesis of element 110 using the  $^{208}\text{Pb}(^{64}\text{Ni},n)$  reaction. Two events, consisting of an implanted heavy atom, followed by the emission of alpha-particles, were obsd. The cross section was 5.5 (+7.3, -2.4) pb. We report upper limit cross sections (1 event) for the prodn. of element 118 in the  $^{208}\text{Pb}(^{86}\text{Kr},n)$  reaction of 0.6 and 0.4 pb for EVR magnetic rigidities of 2.00 and 2.12 Tm. Reanal. of the primary data files from the previous 1999 expt. showed the previously reported element 118 events are not in the original data. We report an upper limit (1 event) for the prodn. of element 112 in the  $^{238}\text{U}(^{48}\text{Ca},3n)$  reaction of .apprch. 1 pb. Measurements of .GAMMA.n/.GAMMA.f for excited No and Hs nuclei are reported. These measurements were made (a) counting the emitted neutrons in these reactions and (b) by measuring the fusion and EVR cross sections.

L13 ANSWER 11 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618337 CAPLUS

TITLE: Teaching nuclear and radiochemistry laboratory at  
Washington University

AUTHOR(S): Sarantities, D. G.

CORPORATE SOURCE: Department of Chemistry, Washington University, St.  
Louis, MO, 63130, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting,  
Boston, MA, United States, August 18-22, 2002 (2002),  
NUCL-025. American Chemical Society: Washington, D.  
C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

Golam Shameem

AB Over the past 30 yr, an extensive list of expts. has been developed that include a broad variety of radiochem. methods and nuclear instrumentation. In a one semester course chem. students perform 12 out of 17 well-structured expts. A list of five addnl. more advanced expts. is also offered to the physics students as part of their measurements lab. The contents and methods of teaching these expts. will be described.

L13 ANSWER 12 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618295 CAPLUS

TITLE: Optically detected magnetic resonance studies of .pi.-conjugated materials

AUTHOR(S): Shinar, J.; Li, G.; Jabbour, G. E.

CORPORATE SOURCE: Department of Physics and Ames Lab, Iowa State University, Ames, IA, 50011, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MTLS-014. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB The electroluminescence- and elec.-detected magnetic resonance (ELDMR and EDMR, resp.) of 2,3,7,8,12,13,17,18-octaethylporphine Pt (PtOEP)-based electrophosphorescent OLEDs is described. At room temp. the measurements yield a neg. (EL-quenching) spin 1/2 resonance similar to those exhibited by fluorescence-based OLEDs. This resonance was concluded to result from magnetic resonance enhancement of the formation of neg. bipolarons at the org.-cathode interface, which enhances the nonradiative quenching of singlet excitons (SEs). It is therefore suspected that similar quenching of SEs by charges at the org./cathode interface may compete significantly with the transfer of the SE energy to TEs in the electrophosphorescent devices as well.

L13 ANSWER 13 OF 1150557 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:618139 CAPLUS

TITLE: Potent noncovalent thrombin inhibitors featuring P3-heterocycles with P1-aminobenzisoxazole arginine surrogates

AUTHOR(S): Semple, J. Edward; Araldi, Gian Luca; Cui, Jingrong Jean; Kemp, Scott; Komandla, Mallareddy; Siev, Daniel V.; Mamedova, Lala; Reiner, John E.; Gibson, Tony S.; Gaudette, John A.; Minami, Nathaniel; Lawrence, C. Maxwell; Anderson, Susanne M.; Bradbury, Annette E.; Nolan, Thomas G.

CORPORATE SOURCE: Department of Medicinal Chemistry, Corvas International, Inc, San Diego, CA, 92121, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-288. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Thrombin (FIIa), a multifunctional serine protease with trypsin-like specificity, plays a central role in the blood coagulation cascade by mediating the conversion of fibrinogen to fibrin and by activation of platelets. The high incidence of heart attack and cardiovascular disease resulting from up-regulation of thrombin represents a leading cause of morbidity and mortality in the industrialized world. Because of this role and other key biol. functions it facilitates in aberrant thrombosis and

hemostasis, thrombin has attracted much attention as a therapeutic target in the pharmaceutical industry. Our quest for potent, selective, non-covalent FIIa inhibitor scaffolds with improved efficacy and oral bioavailability profiles (Bioorg. Med. Chem. Lett. 2002, 12, 743; *ibid.* In press) led us to pursue novel classes of P1-heterobicyclic arginine surrogates. The design, synthesis and *biol.* activity of inhibitors 1 that feature the P1-aminobenzisoxazole residue will be presented.

L13 ANSWER 14 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:618059 CAPLUS  
TITLE: Development of selective CXCR4 inhibitors with strong anti-HIV activity  
AUTHOR(S): Tamamura, Hirokazu; Hiramatsu, Kenichi; Omagari, Akane; Oishi, Shinya; Nakashima, Hideki; Peiper, Stephen C.; Otaka, Akira; Fujii, Nobutaka  
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-207. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English  
AB We have discovered a highly selective CXCR4 antagonist, T22 ([Tyr5, 12, Lys7]-polyphemusin II), and its shortened potent analogs, T140 and TC14012, which strongly inhibit the T-cell line-tropic HIV-1 (X4-HIV-1) infection through their specific binding to a chemokine receptor, CXCR4. CXCR4 is the major co-receptor (second receptor) for the entry of X4-HIV-1 into T-cells. It was found to be difficult to generate a T140-resistant strain *in vitro* as compared to the generation of an HIV strain resistant to other antagonists. Addnl., bifunctional anti-HIV agents based on the specific CXCR4 antagonists (T140 analogs)-3'-azido-3'-deoxythymidine (AZT) conjugation have been synthesized and evaluated, since T140 analogs can possibly work as a carrier of AZT targeting T-cells due to their specific affinity for CXCR4 on T-cells.

L13 ANSWER 15 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:617926 CAPLUS  
TITLE: A Series of Macrocyclic ligands: Synthesis and antitumor activity evaluation *in vitro*  
AUTHOR(S): Kong, Deyuan; Martell, Arthur E.  
CORPORATE SOURCE: Department of Chemistry, Texas A&M University, College Station, TX, 77842-30012, USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-072. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English  
AB A series of aza, oxo, and thia- macrocyclic compds. have been synthesized via 2+2 and 3+2 template reaction using divalent lead ions. Preliminary results show that compd. II (3,6,10,18,22,25-hexaaza-31,32-dihydroxy-14,29-dimethyltricyclo[25,3,1,111,17]dotriaconta -1(30), 12, 14,16(32),27,28-hexaene) has antitumor activities against p388, A549 and Hepa 1-6 tumor cell lines; also it can hydrolyze the supercoiled pBR 322 DNA *in vitro*.



L13 ANSWER 16 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:617907 CAPLUS  
TITLE: Large scale preparation of 5,12  
-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-trione  
AUTHOR(S): Tririya, Gasirat; Zanger, Murray  
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University  
of the Sciences in Philadelphia, Philadelphia, PA,  
19104, USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting,  
Boston, MA, United States, August 18-22, 2002 (2002),  
MEDI-053. American Chemical Society: Washington, D.  
C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English

AB Doxorubicin and daunomycin are structurally related to the group of glycoside antibiotics called anthracyclines which show a very high activity against wide variety of human cancers. Presently, this important antineoplastic agents has been obtained only by microbial fermn. They cannot be produced economically by known synthetic methods; thus, the cost of the drugs is extremely high. These factors have prompted a great interested in development of synthetic routes to these compds. In general the synthesis of these agents is divided into three parts: the synthesis of tetracyclic ring system (aglycon), the synthesis of the aminosugar moiety, and finally the coupling of the two fragments. The main interest has been focus on the synthesis of aglycon. In the search for superior analogs, it was found that the 4-demethoxy analogs of daunomycin and doxorubicin possess increased activity and decreased toxicity. Thus, it is considered appropriate to conc. on the synthesis of precursors such as those leading to the 4-demethoxy aglycon by a simple route and from easily available starting materials. In this research, the precursor of interest is 5,12-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-trione. Currently, two practical and efficient approaches for large scale prepn. of the precursor have been developed: 1. Diels-Alder reaction of 1,4-benzoquinone with 1,3-butadiene, followed by aromatization using acetic acid and dimethylation using di-Me sulfate to give 5,8-dimethoxy-1,4-dihydronaphthalene, which is subsequently epoxidized by using m-CPBA. Epoxide cleavage by Lewis acids such as MgBr<sub>2</sub> etherate is used to construct 5,8-dimethoxy-2-tetralone. 2. Diels-Alder reaction of 1,4-benzoquinone with 2-chloro-1,3-butadiene, followed by aromatization and dimethylation to give 2-chloro-5,8-dimethoxy-1,4-dihydronaphthalene, which is subsequently hydrolyzed by concd. H<sub>2</sub>SO<sub>4</sub> to yield 5,8-dimethoxy-2-tetralone. Since 5,8-dimethoxy-2-tetralone can be prepd. in large quantities, large scale prepn. of the precursor is achieved via Friedel-Crafts reaction of 5,8-dimethoxy-2-tetralone and phthalic anhydride. It is hoped that these syntheses will prove to be a practical approach for prepg. large quantities of the aglycon which will be a useful precursor for further research involving the synthesis of anthracycline antibiotics and development of their analogs with increased activity and decreased toxicity.

L13 ANSWER 17 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:617813 CAPLUS  
TITLE: Novel catalytic reaction of hydrogen as a potential  
new energy source  
AUTHOR(S): Mills, Randell L.; Ray, Paresh; Dong, Jinquan; He,  
Jiliang; Chen, Xuemin; Dhandapani, Bala; Good,  
William; Voigt, Andreas; Hicks, Steve; Nansteel, Mark;  
Dayalan, Ethirajulu; Mayo, Robert  
CORPORATE SOURCE: BlackLight Power Inc, Cranbury, NJ, 08512, USA

Golam Shameem

- SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), INOR-661. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ
- DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English
- AB Extreme UV spectroscopy was recorded on microwave discharges of helium with 2% hydrogen. Novel emission lines were obsd. with energies of  $q-13.6$  eV where  $q=1,2,3,4,6,7,8,9,11,12$ . These lines can be explained as fractional Rydberg states of at. hydrogen formed by the reaction of at. hydrogen with certain catalysts such as  $\text{He}^+$  which ionize at integer multiples of the potential energy of at. hydrogen, 27.2 eV. Fractional-Rydberg-state mol. and mol. ion lines were also recorded. Using alkali catalysts, an inverted Lyman series and the corresponding hydride ions were identified spectroscopically. Novel hydride products were characterized by NMR, ToF-SIMS and XPS. The av. hydrogen atom temp. was 180-210 eV vs.  $\sim 3$  eV for pure hydrogen. Similarly, Te for helium-hydrogen was 28,000 K compared to 6800 K for pure helium. With a microwave input power of 40 W, the thermal output power was measured to be at least 400 W corresponding to a power d. of 40 MW/m<sup>3</sup> and an energy balance of at least  $-5 \times 10^5$  kJ/moleH<sub>2</sub> compared to the enthalpy of combustion of hydrogen of -241.8 kJ/moleH<sub>2</sub>. Direct plasmadynamic conversion to electricity was demonstrated.
- L13 ANSWER 18 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:617800 CAPLUS  
TITLE: Metal-ligand multiple bonds in later, first row complexes  
AUTHOR(S): Dai, Xuliang; Kogut, Elzbieta; Wiencko, Heather L.; Zhang, Libei; Warren, Timothy H.  
CORPORATE SOURCE: Department of Chemistry, Georgetown University, Washington, DC, 20057-1227, USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), INOR-648. American Chemical Society: Washington, D. C.  
CODEN: 69CZPZ
- DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English
- AB The later first row metals are extensively used in coordination complexes that catalyze epoxidn. and aziridination. Proposed key steps in this family of catalytic reactions involve the formal transfer of oxo and imido (nitrene) groups to an olefin via metal-ligand multiply-bound species. To synthetically address these intermediates we have prepd. a family of neutral, monovalent complexes  $[\text{NN}]\text{M}-\text{L}$  ( $\text{M}=\text{Co}, \text{Ni}, \text{Cu}$ ) supported by a bidentate, monoanionic NN donor ligand. These readily isolable species serve as synthons to highly reactive, 12 to 14-electron two-coordinate metal fragments  $\{[\text{NN}]\text{M} \text{ or } [\text{M}]\}$  upon dissocn. of a labile ligand L. Exposure to dioxygen leads to trivalent  $[\text{M}]_2(\mu\text{-O})_2$  species that may be isolated or that further react to give the divalent  $[\text{M}]_2(\mu\text{-OH})_2$ . Treatment with organoazides leads to either four-coordinate bridged imido complexes  $[\text{M}]_2(\mu\text{-NR})_2$  or unique, three-coordinate terminal imido species  $[\text{M}]=\text{NR}$ . We will present reactivity studies with unsatd. substrates and discuss the role of bridged-terminal equil.
- L13 ANSWER 19 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:617757 CAPLUS  
TITLE: Anionic water-soluble .beta.-octafluorinated

porphyrins  
AUTHOR(S): Biffinger, Justin C.; Sun, Haoran; DiMagno, Stephen G.  
CORPORATE SOURCE: Department of Chemistry, University of Nebraska,  
Lincoln, NE, 68588-0304, USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting,  
Boston, MA, United States, August 18-22, 2002 (2002),  
INOR-605. American Chemical Society: Washington, D.  
C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English  
AB The first sulfonated water-sol. .beta.-fluorinated porphyrins  
[5,10,15,20-tetrakis-(4-sulfonatophenyl)-2,3,7,8,12  
,13,17,18-octafluoroporphyrin (1) and 5,10,15,20-tetrakis-(2,6-difluoro-3-  
sulfonatophenyl)-2,3,7,8,12,13,17,18-octafluoroporphyrin(2)]  
have been prep'd. The free-base porphyrin is the major species between pH  
3-11 for (1) and between pH 0-9 for (2). Various transition metals were  
successfully inserted [Zn(II), Co(II), Mn(III), Fe(III), Rh(III)]. The  
rhodium porphyrins of (1) and (2) were alkylated in water from the  
rhodium(I) comp'd. and iodomethane. Co(II) and Mn(III) oxidn. chem. in  
aerobic and anaerobic solns. will also be discussed along with their  
electrochem. behavior.

L13 ANSWER 20 OF 1150557 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:617723 CAPLUS  
TITLE: Unusual chemistry of dodecaalkoxy-closo-dodecaborate(-  
2)ions  
AUTHOR(S): Hawthorne, M. Frederick; Huertas, Ramon; Peymann,  
Toralf; Knobler, Carolyn B.  
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University  
of California, Los Angeles, Los Angeles, CA, 90095,  
USA  
SOURCE: Abstracts of Papers, 224th ACS National Meeting,  
Boston, MA, United States, August 18-22, 2002 (2002),  
INOR-571. American Chemical Society: Washington, D.  
C.  
CODEN: 69CZPZ  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English

AB Perhydroxylation of [closo-B12H12]2- produces the [closo-B12(OH)12  
]2-, 1, which serves as a precursor for carboxylate ester and alkoxyl  
closomers, [closo-B12(OCOR)12]2-and [closo-B12(OCH2R)12  
]2-, 2, resp. The alkoxyl derivs. are produced by the reaction of an  
alkyl halide with 1 in the presence of diethylisopropyl amine. The one-  
and two-electron oxidn. of 26-electron 2 produces the corresponding  
25-electron radical anion, 3, and the 24-electron neutral species, 4,  
resp. A variety of alkoxyl derivs. have been investigated and their  
electrochem. behavior correlated with their structures. Back-bonding of  
the nonbonded electrons present on the alkoxyl oxygen atoms with the  
electron deficient hypercloso borane cage stabilizes 3 and 4. The  
structure of the stable electron deficient 4species displays a Jahn-Teller  
distortion to D3d symmetry. The reactions, structures and bonding of  
these novel closomer species will be.

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Golam Shameem

# PATENT COOPERATION TREATY

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## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
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<b>Date of mailing</b> (day/month/year) 07 March 2001 (07.03.01)	
<b>International application No.</b> PCT/US00/16319	<b>Applicant's or agent's file reference</b> X-12420
<b>International filing date</b> (day/month/year) 11 July 2000 (11.07.00)	<b>Priority date</b> (day/month/year) 19 July 1999 (19.07.99)
<b>Applicant</b> LIN, Ho-Shen et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
24 January 2001 (24.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b> C. Cupello
<b>Facsimile No.:</b> (41-22) 740.14.35	<b>Telephone No.:</b> (41-22) 338.83.38